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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

SMITHKLINE BEECHAM PLC, SB PHARMCO PUERTO RICO INC., and SMITHKLINE BEECHAM CORPORATION, Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	Civil Action Nos. 04-215 and 05-536 (NLH) (JS)

SKB'S PROPOSED MEMORANDUM OPINION

HILLMAN, District Judge.

In these consolidated actions, Plaintiffs Beecham PLC, SB Pharmco Puerto Rico Inc. and SmithKline Beecham Corporation (collectively, "SKB") have sued Defendant Teva Pharmaceuticals USA, Inc. ("Teva") under 35 U.S.C. § 1 *et seq.* and 35 U.S.C. § 271(e)(2) and § 281, for infringing U.S. Patent No. 5,002,953 ("the '953 Patent").

Presently before the Court is SKB's motion for summary judgment on Teva's defense that Claims 42 and 43 the '953 Patent are invalid for obviousness under 35 U.S.C. § 103. Teva presents its obviousness defense through a single expert witness, Dr. Lemont Kier. As explained below, the issue before the Court reduces to whether Dr. Kier's testimony, when considered in light of the applicable legal standards and the undisputed record evidence, including the prior art references on which Dr. Kier relies, would establish by clear and convincing evidence that Claims 42 and 43 are obvious. The Court has considered the parties' initial, opposition, reply, and surreply briefs on this motion, and it heard oral argument on June 8, 13 and 28, 2007. For the reasons expressed below, SKB's motion for summary judgment is **GRANTED.**

I. BACKGROUND FACTS

A. Overview of the Claims 42 and 43 of the '953 Patent

The sole inventor of the '953 Patent is Mr. Richard Hindley. Ex. 1 ('953

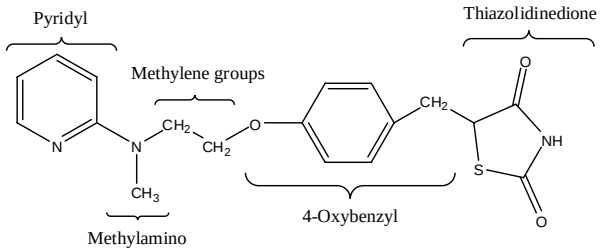
Patent).[1] The U.S. application for the '953 Patent was filed on December 27, 1989, and it claimed priority to three United Kingdom patents, the earliest filed on September 4, 1987. *Id.* The patent issued on March 26, 1991. Plaintiffs are the assignee or licensees of the '953 Patent. *Id.*

The '953 Patent relates to certain chemical compounds known as "substituted thiazolidinedione derivatives" that show "improved blood-glucose lowering activity and are therefore of potential use in the treatment and/or prophylaxis of hyperglycaemia and are of particular use in the treatment of Type II diabetes." *Id.*, col. 1, lines 6-7, 21-24. Thiazolidinedione derivatives -- so-called because they contain a thiazolidinedione or "TZD" ring -- are commonly referred to as "TZDs." Claim 1 of the '953 Patent claims a set, or "genus," of TZD compounds that are described by Formula (I) in the patent. *Id.*, col. 38, lines 15-62. Claims 2-51 of the '953 Patent claim specific TZD compounds that come within the scope of Formula (I). *Id.*, col. 38, line 63 to col. 44, line 66. The claims at issue in this motion are Claims 42 and 43.

Claim 42 of the '953 Patent claims the compound 5-(4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl)2,4-thiazolidinedione, which is known as rosiglitazone, "and/or a pharmaceutically acceptable salt thereof." *Id.*, col. 43,

[1] "Ex. __" refers to Exhibits attached to the Declaration and Supplemental Declaration of Bindu Donovan in Support of SKB's Motion for Summary Judgment of Nonobviousness of Claim 42 and 43 of the '952 Patent.

lines 58-62. Rosiglitazone has the following structure:

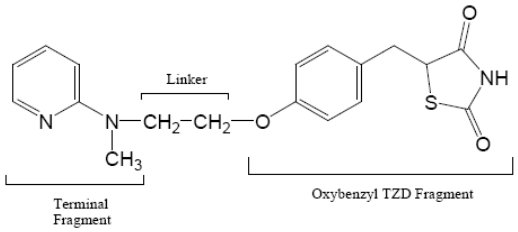


Although the structure of rosiglitazone is undisputed, the parties describe the structural elements of rosiglitazone differently. As shown above, SKB describes the rosiglitazone molecule as containing the following elements (from left to right)[2]. First, at the far left is an unsubstituted 2-pyridyl ring. (The "2" in "2-pyridyl" describes the position of attachment of the ring to the remainder of the molecule, counting from the atom in the ring with the highest atomic weight, which is assigned the "1" position. Here, the nitrogen in the ring has the highest atomic weight, and so the ring is attached to the rest of the molecule at the "2" position. The ring is "unsubstituted" because only hydrogen atoms – which are, by convention, not shown in the drawing – and no other atoms are attached to the carbon atoms in the ring.) Second, to the right of the 2-pyridyl ring, there is a methylamino group, *i.e.*, a nitrogen atom with an attached methyl (CH_3) group. Third, there are two methylene (CH_2) groups. Next, there is an oxybenzyl group, consisting of an oxygen atom (O) connected to a benzene ring which is connected

[2] While references are made to the left and right sides of the molecule for convenience, in reality there is no left or right side to a molecule because the molecule is not fixed in space and is three-dimensional.

to a methylene (CH_2) group. Finally, on the far right side of the molecule, there is a TZD ring. SKB Br. at 9; SKB Rule 56.1 ¶ 30; Taylor Decl. ¶¶ 21-22.

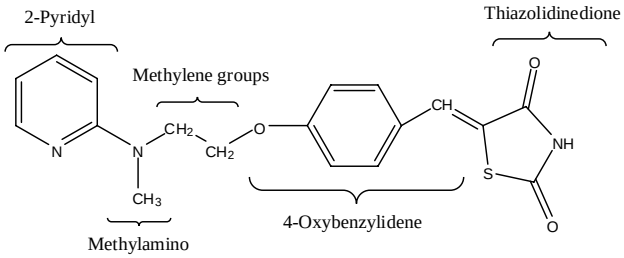
Teva, on the other hand, describes rosiglitazone as containing (from left to right): 1) a "terminal fragment" consisting of a methylamino substituted 2-pyridyl group; 2) a "linker region" containing two methylene groups; and 3) an "oxybenzyl TZD fragment," as shown below:



Teva Rule 56.1 ¶ 30; Kier Decl. ¶ 29. According to Teva, a factual dispute exists concerning how to characterize the structural elements of rosiglitazone. *See, e.g.*, Teva Br. at pp. 5-6. Although Teva's use of the terms "terminal fragment," "linker region," and "oxybenzyl TZD fragment" are important to understanding its arguments, described below, the Court concludes that the parties' differing characterizations of the elements of rosiglitazone do not create a material issue of fact.

Claim 43 of the '953 patent claims the compound 5-(4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione, known as dehydrorosiglitazone or "DRG." DRG is a precursor – or "intermediate" – chemical compound used to make rosiglitazone. Ex. 1 ('953 Patent) at col. 35,

lines 5-26; Teva Rule 56.1 ¶ 24. As shown below, the sole two-dimensional structural difference between rosiglitazone and DRG is the bond between the TZD ring and the oxybenzyl group. In DRG, this bond is a double bond, and in rosiglitazone, it is a single bond. Teva Rule 56.1 ¶ 25.



B. Procedural Background

SKB makes and sells Avandia® and Avandamet®, two prescription pharmaceutical products approved by Food and Drug Administration ("FDA") for the treatment of Type II diabetes. The active ingredient in Avandia® is rosiglitazone maleate, the maleate salt form of the compound rosiglitazone. Avandamet® is a combination drug product which includes rosiglitazone maleate and another antidiabetic agent, metformin hydrochloride. As discussed above, Claim 42 of the '953 Patent covers rosiglitazone "and/or a pharmaceutically acceptable salt thereof." The parties agree that Claim 42 covers rosiglitazone maleate. Teva Rule 56.1 ¶¶ 22-23.

Teva filed separate Abbreviated New Drug Applications ("ANDAs"), Nos. 76-747 and 77-337, seeking approval from the FDA to market generic versions of Avandia® and Avandamet®, respectively. In connection with those ANDAs, Teva

certified to the FDA that the '953 Patent is invalid, unenforceable, or will not be infringed by the products it seeks authority to market. On December 9, 2003 (ANDA No. 76-747) and December 20, 2004 (ANDA No. 77-337), Teva sent SKB "Paragraph IV" letters which notified SKB of its certifications to the FDA and set out the basis for Teva's legal assertions about the '953 Patent. Ex. 6 (Avandia® Para. IV Letter) and Ex. 7 (Avandamet® Para. IV Letter). Pursuant to 35 U.S.C. § 271(e)(2)(A), Teva's certifications constituted an act of infringement, giving SKB the right to initiate suit for infringement of the '953 Patent. Civil Action Nos. 04-215 and 05-536 followed.

SKB alleges that the products that are the subject of Teva's ANDAs will infringe Claims 42 and 43 of the '953 Patent, if and when they are marketed. Teva has stipulated that those products will literally infringe Claim 42, but it disputes that they will infringe Claim 43. Ex. 12 ('953 Patent Stip., 04-215) at ¶¶ 2, 8; Ex. 55 ('953 Patent Stip, 05-536) at ¶¶ 2,8. (Whether the products will infringe Claim 43 is the subject of a separate summary judgment motion before the Court.) However, Teva alleges that both Claims 42 and 43 are invalid because they are obvious under 35 U.S.C. §103. SKB has moved for summary judgment on Teva's defense that Claims 42 and 43 of the '953 Patent are obvious.

II. LEGAL STANDARDS APPLICABLE TO SKB's MOTION

A. Summary Judgment

A summary judgment motion should be granted when the moving party demonstrates that there is no genuine issue as to any material fact. Fed. R. Civ. P. 56 (c); *Celotex Corp. v. Catrett*, 477 U.S. 317, 322-23 (1986). When considering the evidence presented in support of, and in opposition to, a summary judgment motion, "all justifiable inferences are to be drawn in [the nonmovant's] favor." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255 (1986).

"Summary judgment procedure is properly regarded not as a disfavored procedural shortcut, but rather as an integral part of the Federal Rules as a whole, which are designed 'to secure the just, speedy and inexpensive determination of every action.'" *Celotex*, 477 U.S. at 327. "Summary judgment is as appropriate in a patent case as in any other." *Avia Group Int'l, Inc. v. L.A. Gear California, Inc.*, 853 F.2d 1557, 1561 (Fed. Cir. 1988) (citations omitted)).

A summary judgment motion raises the threshold inquiry of whether there is a need for a trial, *i.e.*, "whether there is a genuine issue for trial." *See Anderson*, 477 U.S. at 249 ("at the summary judgment stage the judge's function is not himself to weigh the evidence and determine the truth of the matter but to determine whether there is a genuine issue for trial"). There is a genuine issue for trial "if the evidence is such that a reasonable jury could return a verdict for the

nonmoving party." *Id.* at 248. Conversely, "there is no issue for trial unless there is sufficient evidence favoring the nonmoving party for a jury to return a verdict for that party." *Id.* at 249.

It is not enough for the nonmovant to present a mere scintilla of evidence in opposition to a summary judgment motion. *Id.* at 251. Rather, the nonmovant must present "significant probative evidence" that would "require a jury or judge to resolve the parties' differing versions of the truth at trial." *Id*. at 248-249. In addition, the court must decide a summary judgment motion on the basis of all of the undisputed evidence. While the nonmovant is entitled to have the evidence viewed in a light most favorable to it, it cannot ask the court to disregard undisputed admissible evidence. As the Supreme Court stated in *Reeves v. Sanderson Plumbing Prods.*, 530 U.S. 133, 151 (2000), "[T]he court should the record as a while. … [T]he court should give credence to the evidence favoring the nonmovant as well as that 'evidence supporting the moving party that is uncontradicted and unimpeached ….'" (quoting Wright & A. Miller, Federal Practice and Procedure § 2529, p. 300 (2d ed. 1995)).

Because the summary judgment issue is whether there is a need for a trial, a court deciding a summary judgment motion must view the evidence presented by the parties in support of, and in opposition to, the motion through the prism of the substantive evidentiary burdens that each party would bear at a trial on the merits.

See Anderson, 477 U.S. at 252 ("[W]e are convinced that the inquiry involved in a ruling on a motion for summary judgment . . . necessarily implicates the substantive evidentiary standard of proof that would apply at the trial on the merits"); *Northwestern Mut. Life Ins. Co. v. Babayan*, 430 F.3d 121, 137 (3d Cir. 2005) ("At the summary judgment stage, the [non-movant's] burden … is commensurately high because the court must view the evidence presented in light of the substantive burden at trial"); *Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1062 (Fed. Cir. 2005) ("[O]n summary judgment, the court holds the parties to the same evidentiary burden they would have faced at trial.").

Here, because an issued patent is entitled to a presumption of validity, 35 U.S.C. § 282, the patent can be found invalid only if invalidity has been proven by clear and convincing evidence. *Takeda Chem. Indus., Ltd. v. Alphapharm Pvt., Ltd.*, No. 06-1329, 2007 WL 1839698, at *3 (Fed. Cir. June 28, 2007). *See also State Contracting & Eng'g Corp. v. Condotte Am, Inc.*, 436 F.3d 1057, 1067 (Fed. Cir. 2003) ("A party seeking to establish that particular claims are invalid must overcome the presumption of validity in 35 U.S.C. § 282 by clear and convincing evidence"). With respect to a defense of obviousness, the Federal Circuit has stated that "[e]ach fact forming the factual foundation upon which the court bases its ultimate conclusion regarding the obviousness of the claimed subject matter … must be established by clear and convincing evidence." *Ashland Oil, Inc. v. Delta*

Resins & Refractories, Inc., 776 F.2d 281, 292 (Fed. Cir. 1985). Thus, Teva's opposition to SKB's motion for summary judgment must be viewed in light of its burden to establish obviousness by clear and convincing evidence.

In *Celotex*, the Supreme Court recognized that, "the plain language of Rule 56(c) mandates the entry of summary judgment . . . against a party who fails to make a showing sufficient to establish the existence of an element essential to that party's case, and on which that party will bear the burden of proof at trial." *Celotex*, 477 U.S. at 322-23. "[W]ith respect to an issue on which the nonmoving party bears the burden of proof, . . . the burden on the moving party may be discharged by 'showing' -- that is, pointing out to the district court -- that there is an absence of evidence to support the nonmoving party's case." *Celotex*, 477 U.S. at 325.

In sum, if Teva has presented admissible evidence in opposition to SKB's motion which, when viewed in a light most favorable to Teva but in context with the undisputed facts, would prove by clear and convincing evidence that the '953 Patent is obvious, the Court must deny SKB's motion for summary judgment. If the Court concludes that Teva's evidence, even when viewed in this manner, would not establish that the '953 Patent is obvious by clear and convincing evidence, then SKB's motion must be granted.

B. Obviousness Under 35 U.S.C. § 103(a)

A patent is obvious under 35 U.S.C. § 103(a) "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a).

Whether an invention is obvious under 35 U.S.C. § 103 is a legal determination based upon underlying factual inquiries. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1745 (2007) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966)); *Takeda*, 2007 WL 1839698, at *3. The analytical framework for applying the statutory language of § 103 was outlined by the Supreme Court in *Graham*, and reaffirmed in *KSR*:

> Under § 103 the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

See KSR 127 S. Ct. at 1734 (quoting *Graham*, 383 U.S. at 17-18).

Obviousness is evaluated from the perspective of a hypothetical person of ordinary skill in the art who is presumed to know all of the prior art, but is neither a genius nor an innovator. *Janssen Pharmaceutica N.V. v. Mylan Pharms., Inc.*, 456

F. Supp. 2d 644, 653 (D.N.J. 2006). *See also Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed.Cir. 1985) ("A person of ordinary skill in the art is also presumed to be one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights, it makes no difference which"). Nevertheless, "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton." *KSR*, 127 S. Ct. at 1742.

Moreover, evaluations of obviousness must not rely upon hindsight:

> Almost any invention, no matter how nonobvious at the time, will appear obvious when looking backward from the solution. It is for that reason that "[c]are must be taken to avoid hindsight reconstruction *by using 'the patent in suit as a guide through the maze of prior art references*, combining the right references in the right way so as to achieve the result of the claims in suit.'"

Id. at 662 (emphasis in original) (quoting *Grain Processing Corp. v. Am. Maize-Prods. Co.*, 840 F.2d 902, 907 (Fed. Cir. 1988). *See also KSR*, 127 S. Ct. at 1742 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning"); *Eisai Co. v. Teva Pharms. USA, Inc.*, No. 03 Civ. 9223 (GEL), 2006 WL 2872615, at *2 (S.D.N.Y. October 6, 2006) ("The decision maker must step back in time to before the moment of actual invention, and out of the actual inventor's shoes into those of a hypothetical, ordinary skilled person who has never seen the invention").

In the case of a patent for a chemical compound, an obviousness defense has

two key elements. *First*, the Supreme Court stated in *KSR* that where the claimed subject matter involves more than the mere substitution of one known element for another, "it will be necessary for a court . . . to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *KSR*, 127 S. Ct. at 1740-41. "To facilitate review, this analysis should be made explicit." *Id.* at 1741.

In a post-*KSR* decision, the Federal Circuit applied that standard in a case much like this one, holding that in the case of a patent for the chemical compound pioglitazone (which will be discussed later), the "structural similarity between claimed and prior art subject matter" creates "a *prima facie* case of obviousness" only "where the prior art gives reason or motivation to make the claimed compositions." *Takeda*, 2007 WL 1839698, at *4 (quoting *In re Dillon*, 919 F.2d 919, 692 (Fed. Cir. 1990) (*en banc*). "Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish a prima facie obviousness of a new claimed compound." *Takeda*, 2007 WL 1839698, at *5. Teva must therefore show, by clear and convincing evidence, that the prior art or common knowledge would have provided a reason, at the time of the invention, for a person of ordinary skill in the art to modify a known compound to create the novel compound rosiglitazone.

Second, to establish obviousness, Teva must show that at the time of the invention, the person of ordinary skill in the art would have had a "reasonable expectation of success" that making the claimed combination would have resulted in the claimed invention.[3] *See Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, No. 05-1490, 05-1551, 2007 WL 1964863, at *15 (Fed. Cir. Jul. 9, 2007) ("[T]he burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, and would have had a reasonable expectation of success in doing so"); *Pfizer v. Apotex*, 480 F.3d 1348, 1361 (Fed. Cir. 2007) (same); *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343 (Fed. Cir. 2000) ("'[A] reasonable expectation of success, not absolute predictability, supports a conclusion of obviousness'") (quoting *In re Longi*, 759 F.2d 887, 896 (Fed. Cir. 1985). To establish obviousness, therefore, Teva must show that a person of skill in the art would have had a reasonable expectation of success that rosiglitazone would be useful in the treatment of Type II diabetes. *See Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*,

[3] Where a defendant establishes a *prima facie* case of obviousness, the patent holder can rebut the showing by introducing evidence of secondary considerations of non-obviousness, such as unexpected results, commercial success, long felt but unsolved needs, failure of others, and copying. *Graham*, 383 U.S. at 18; *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 667 (Fed. Cir. 2000). For purposes of its summary judgment motion, SKB does not rely on any secondary considerations of nonobviousness, and the court has not considered them.

417 F. Supp. 2d 341, 371-72 (S.D.N.Y. 2006) (success was "a non-toxic, effective treatment for diabetes"); *Yamanouchi*, 231 F.3d at 1345 ("The success of discovering famotidine was not discovering one of the tens of thousands of compounds that exhibit baseline H_2 antagonist activity. Rather, the success was finding a compound that had high activity, few side effects, and lacked toxicity"); *Eli Lilly v. Zenith Goldline Pharms.*, 364 F. Supp. 2d 820, 905 (S.D. Ind. 2005) ("Defendants have failed to prove by clear and convincing evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in developing a safe, effective, atypical antipsychotic drug by making the changes to the prior art that they propose … "), *aff'd*, 471 F.3d 1369 (Fed. Cir. 2006).

C. Legal Principles Applicable to Dr. Kier's Opinions

As stated previously, Teva's sole witness on the issue of obviousness is Dr. Lemont Kier, who is Professor of Medicinal Chemistry at the School of Pharmacy, Virginia Commonwealth University. Kier Decl. ¶ 7. Dr. Kier has expertise in theoretical approaches to drug design, including developing molecular orbital theory, methods for molecule description and structure modeling. Kier Decl. ¶¶ 6-8. His testimony must be considered in the light most favorable to Teva. Fed. R. Civ. P. 56. That does not mean, however, that the Court must or can uncritically accept Dr. Kier's conclusions, for that would imply that summary judgment could never be granted if the nonmoving party presented expert testimony in support of

its position. That is clearly not the law. *Heller v. Shaw Indus., Inc.*, 167 F.3d 146, 152 (3d Cir. 1999) ("even if expert testimony is admitted, summary judgment might be warranted if a party has still failed to present sufficient evidence to get to the jury."); *Network Commerce, Inc. v. Microsoft Corp.*, 422 F.3d 1353, 1363 (Fed. Cir. 2005) (affirming district court summary judgment ruling despite expert testimony from the non-moving party); *Dynacore Holdings Corp. v. U.S. Philips Corp.*, 363 F.3d 1263, 1278 (Fed. Cir. 2004) (same); *Arthur A. Collins, Inc. v. Northern Telecom Ltd.*, 216 F.3d 1042, 1047 (Fed. Cir. 2000) (same).

Dr. Kier's testimony is to be considered in light of several established legal principles. To begin, his testimony must be considered as a whole and in light of the entire record. *Reeves*, 530 U.S. at 150 (in deciding the appropriateness of summary judgment "the court must review the record taken as a whole") (internal quotations omitted); *Abramson v. William Paterson College*, 260 F.3d 265, 276 (3d Cir. 2001); ("the court should not consider the record solely in piecemeal fashion, giving credence to innocent explanations for individual strands of evidence").

If the Court concludes that an expert's conclusions are "not supported by sufficient facts … , or when indisputable facts contradict or otherwise render the opinion unreasonable," they may be discounted. *Brooke Group Ltd. v. Brown and Williamson Corp.*, 509 U.S. 209, 242 (1993); *see also In re Apple Computer Sec. Litig.*, 886 F.2d 1109, 1116 (9th Cir. 1989) ("where the evidence is as clear as that

in this record, the court is not required to defer to the contrary opinion of plaintiffs' 'expert'"). Moreover, courts may disregard testimony offered in opposition to a summary judgment motion that contradicts earlier deposition testimony. *Anchor Wall Sys. v. Rockwood Retaining Walls, Inc.*, 340 F.3d 1298, 1314 (Fed. Cir. 2003) (affirming district court decision to strike the declaration of an expert that was inconsistent with prior sworn testimony); *Hackman v. Valley Fair*, 932 F.2d 239, 241 (3rd Cir. 1991) ("When, without a satisfactory explanation, a nonmovant's affidavit contradicts earlier deposition testimony, the district court may disregard the affidavit").

In addition, a court may disregard a conclusory opinion that a patent claim is obvious if that conclusion is contradicted by the very prior art on which the expert relies. Earlier this year, the Federal Circuit held that an expert opinion that conflicts with the clear teachings of the prior art cannot defeat a motion for summary judgment. *Advanced Tech. Materials, Inc. v. Praxair, Inc.*, No. 2006-1540, 2007 WL 1158103, at *2 (Fed. Cir. April 19, 2007) (finding that an expert's opinion did not raise a genuine issue of material fact regarding the teachings in the prior art because it "lacked logical continuity").

This holding appears to be a narrow application of two principles long-established in patent law. The first is that a prior art reference "must be considered in its entirety, *i.e.*, as a *whole*, including portions that would lead away from the

invention in suit." *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568 (Fed. Cir. 1987) (citation omitted; emphasis in original). *See also Ashland*, 776 F.2d at 296 ("A reference, however, must have been considered for all it taught, disclosures that diverged and taught away from the invention at hand as well as disclosures that pointed towards and taught the invention at hand."). The second principle is that an expert's opinion cannot satisfy the clear and convincing evidentiary standard if it lacks support in the factual record. *Invitrogen*, 429 F.3d at 1080 ("A party does not manufacture more than a merely colorable dispute simply by submitting an expert declaration asserting that something is black when the moving party's expert says it is white; there must be some foundation or basis for the opinion"); *Ashland*, 776 F.2d at 294 ("Lack of factual support for expert opinion going to factual determinations, however, may render the testimony of little probative value in a validity determination"). Putting these long-established principles together leads to the conclusion that, as stated by the Federal Circuit in *Advanced Tech. Materials*, expert opinions which the court concludes are contradicted by the prior art otherwise relied on, cannot defeat summary judgment.

Finally, summary judgment is appropriate if there exists a failure of proof on a critical element of a claim or defense on which the nonmoving party bears the burden of proof. *See Celotex*, 477 U.S. at 322-23; *Ortho-McNeil Pharm., Inc. v. Mylan Labs. Inc.*, Nos. 04-1689, 06-757, 06-5166, 2007 WL 432792, at *7 (D.N.J.

Feb. 5, 2007) (granting plaintiff's motion for partial summary judgment on defendant's defense of patent invalidity due to obviousness because of a "failure of proof concerning an essential element of the nonmoving party's case); *Eisai*, 2006 WL 2872615, at *3 (granting plaintiffs' motion for summary judgment of validity of their patent against defendant's obviousness counterclaim on the ground that defendant Teva's submissions were "insufficient to sustain a judgment by clear and convincing evidence that the ordinary skilled person would have made the particular combination . . ., reasonably expecting [the invention] to result").

III. Teva's Obviousness Theory

A. The Prior Art Relied Upon by Teva

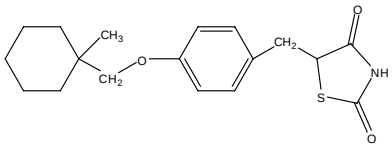
Teva relies primarily on a series of prior art references that emanated from research concerning TZDs conducted by Takeda Chemical Industries, Ltd. ("Takeda"), each of which disclose, among other things, TZD compounds having a 5-(4-oxybenzyl)-thiazolidine-2,4-dione moiety, to which are attached a wide array of structural groups. The principal references on which Teva relies are: (a) Sohda *et al.*, "Antidiabetic Agents II - Synthesis of 5-[4-(1-methylcyclohexylmethoxy)-benzyl]-thiazolidine-2,4-dione (ADD-3878)," Chem. Pharm. Bull. 30 (10):3580-3600 (1982) ("Sohda II,"); (b) U.S. Patent No. 4,461,902 ("the '902 Patent"); and (c) U.S. Patent No. 4,687,777 ("the '777 Patent"). Kier Decl. ¶¶ 18, 20, 31; Ex. 22, 23 and 24. Each is described below.

1. Sohda II

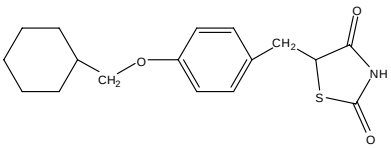
Published in 1982, the Sohda II article discloses 101 different TZD compounds and generally describes, on a scale of 1 to 4, their relative blood glucose-lowering activity and plasma triglyceride-lowering activity. Sohda II does not disclose the precise activity values for its relative rankings of the compounds. Although Sohda II's narrative refers at times to the relative toxicities of a few compounds, it does not provide the specific toxicity data or explain how the toxicity studies were performed. Ex. 22 (Sohda II) at Table I to VII, Table I note *e*; Teva Rule 56.1 ¶ 75.

Sohda II concludes that three compounds, identified as compounds 49, 47 and 59, "exhibited the most favorable profiles in terms of activity and toxicity." Ex. 22 (Sohda II) at p. 3589; Teva Rule 56.1 ¶ 77. Of these three "most favorable" compounds, Sohda II calls out only compound 49, also known as ciglitazone, as having "potential utility as an antidiabetic drug." Ex. 22 (Sohda II) at p. 3589; Teva Rule 56.1 ¶ 88.

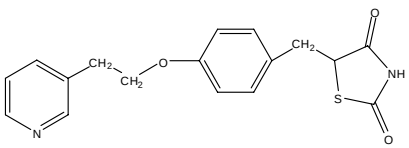
Compounds 49 (ciglitazone), 47 and 59 are shown below:



Compound 49 - ciglitazone



Compound 47



Compound 59

None of these compounds contain the methylamino group of rosiglitazone. Unlike rosiglitazone, compounds 49 (ciglitazone) and 47 have only one methylene

group between the left-hand ring and the oxybenzyl TZD group. None of the compounds has a 2-pyridyl ring like rosiglitazone; the "terminal fragments" in compounds 49 (ciglitazone) and 47 are a substituted and unsubstituted cyclohexyl group, respectively, and the terminal fragment in compound 59 is a 3-pyridyl ring. Teva Rule 56.1 ¶¶ 79-80, 82-83, 85-86.

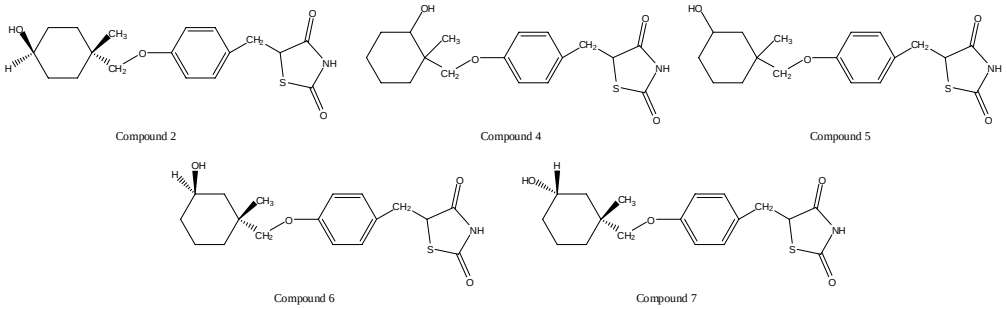
Sohda II states that "a series of compounds bearing less lipophilic groups (*i.e.*, pyridylalkyl, aminoalkyl, *etc.*) instead of aralkyl or alkyl groups was next investigated. Although compounds 56, 57, 58, 59 and 63 . . . showed potent activities, they, especially 57 and 58, caused considerable increases in body weight and brown fat weight." Ex. 22 (Sohda II) at p. 3589. Compounds 57 and 58 – both in the "less lipophilic group" -- are the only two compounds in Sohda II that contain a 2-pyridyl ring, Ex. 22 (Sohda II) at Table IV, but neither of them were identified as a compound having "the most favorable profile[] in terms of activity and potency" or as having "potential utility as an antidiabetic drug." Ex. 22 (Sohda II) at pp. 3588-89; Teva Rule 56.1 ¶ 90.

2. The '902 Patent

Two of the co-authors of Sohda II filed a patent application in 1982 that matured into the '902 Patent, which was assigned to Takeda. Ex. 23 ('902 Patent); Ex. 22 (Sohda II); Teva Rule 56.1 ¶ 106. The '902 Patent discloses and claims "hydroxyciglitazones," compounds in which a hydroxy (-OH) group is attached at

various positions of the methylcyclohexyl group (the left-hand ring) of ciglitazone. Ex. 23 ('902 Patent); Teva Rule 56.1 ¶ 105.

The '902 Patent contains a table (in column 7) that shows test results of ciglitazone (compound 1) and the following five hydroxyciglitazone compounds:



Ex. 23 ('902 Patent) at col. 7, lines 1-22.

These compounds differ only with respect to where the hydroxy (OH-) group is attached to the methylcyclohexyl ring on the left-hand side. (By convention, carbon atoms that form the angles in the rings are not identified, and hydrogen atoms attached to those carbon atoms are also not shown.) Ex. 23 ('902 Patent) at col. 7, lines 1-22; Teva Rule 56.1 ¶ 107. And, in the case of Compounds 6 and 7, the only difference is the spatial orientation of the hydrogen (H) and the hydroxy (OH) group attached to the methylcyclohexyl group. Taylor Decl. ¶ 65. (The solid and hashed lines in compound 6 indicate that in three-dimensional space, the OH group would jut out from the plane of the paper on which the diagram is drawn, while the hydrogen is beneath the paper; in compound 7, the three-dimensional orientation of the OH and H groups is the opposite. *Id.*)

These compounds were tested in mice to determine their blood glucose-lowering activity relative to ciglitazone. Ex. 23 ('902 Patent) at col. 6, lines 56-68. The results are displayed in the table in column 7 of the '902 Patent.

Test Compound	Hypoglycemic Activity
Compound (1) (Ciglitazone)	100
Compound (2)	118
Compound (4)	114
Compound (5)	148
Compound (6)	369
Compound (7)	125

Ex. 23 ('902 Patent) at col. 7, lines 1-22. All of the hydroxyciglitazone compounds shown in the table in the '902 Patent exhibited greater blood glucose lowering activity than ciglitazone, *i.e.*, compound 1. Teva Rule 56.1 ¶ 108. However, the structurally similar compounds 2, 4, 5, 6 and 7 showed very different activities, with compound 6 exhibiting glucose-lowering activity 369% greater than that of ciglitazone. Ex. 23 ('902 Patent) at col. 7, lines 1-22; Teva Rule 56.1 ¶ 110.

3. The '777 Patent

In January 1986, two Takeda researchers, including one who was both a co-author of Sohda II and a co-inventor of the '902 Patent, filed the application for the '777 Patent, which issued on August 18, 1987. Ex. 24 ('777 Patent") Ex. 22 (Sohda II); Ex. 23 ('902 Patent); Teva Rule 56.1 ¶ 126. The '777 Patent describes TZD compounds having 2-pyridyl groups on the left-hand side which are substituted with methyl (CH_3) or ethyl (CH_2CH_3) groups. Ex. 24 ('777 Patent) at Table 1 (cols. 5-6); Teva Rule 56.1 ¶ 124. The '777 Patent specifically discloses, as

Compound (I), the compound known as pioglitazone, the active ingredient in Takeda's commercialized product Actos®. *See generally*, *Takeda*, 2007 WL 1839698, at *4 (upholding the district court's finding that the defendant generic companies had failed to show that the claim to pioglitazone in the '777 Patent is invalid as obvious).

Column 1 of the '777 Patent refers to the compounds disclosed in Sohda II and the '902 Patent and states that "[t]hose compounds, however, have not yet been put to practical use. As the reasons, (1) insufficient activities or/and (2) serious toxicities may be mentioned." Ex. 24 ('777 Patent) at col. 1, lines 18-28; Ex. 25 (Sohda IV); Teva Rule 56.1 ¶¶ 121, 152-154.

Table 1 of the '777 Patent presents the results of biological tests done using pioglitazone (compound I), ciglitazone (compound (a)), and four methylpyridyl TZDs (*i.e.*, TZD compounds having 2-pyridyl groups on the left-hand side that are substituted with a methyl (CH_3) group). Ex. 24 ('777 Patent) at col. 4, line 31-col. 5, line 13, Table 1 (cols. 5-6). The four methylpyridyl TZDs differ from each other only with respect to where the methyl group is attached to the pyridyl ring, *i.e.*, the methyl group is attached to the 3, 4, 5, and 6 positions of the pyridyl ring of compounds e, d, c, and b, respectively. Taylor Decl. ¶¶ 71-72. These compounds are shown below:

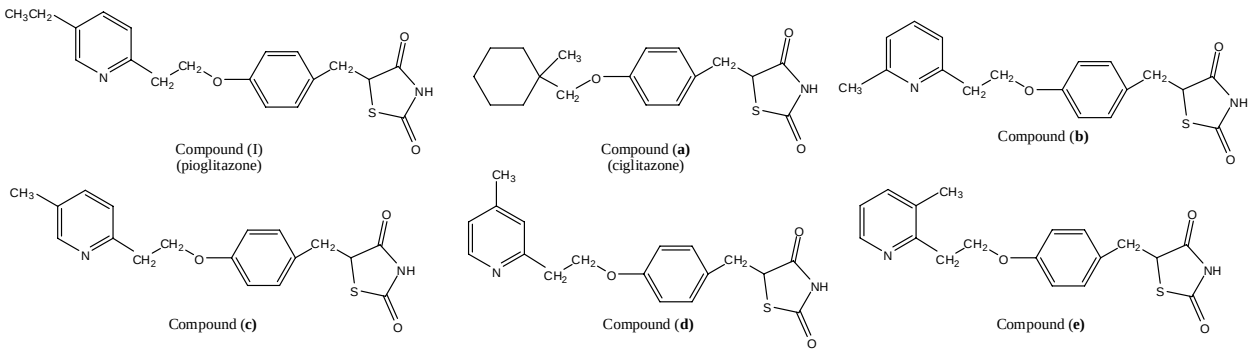


Table I also shows the hypoglycemic- and triglyceride-lowering activities, as well as toxic effects, that each compound exhibited in tests done in mice and rats. Ex. 24 ('777 Patent) at col. 4, line 31-col. 5, line 13, Table 1 (cols. 5-6).

The '777 Patent

	Blood Glucose (ED_{25}) mouse	Two-weeks Toxicity (rat, %)					
		Liver weight		Heart weight		number of erythrocyte	
		♂	♀	♂	♀	♂	♀
Compound (b)	4	+3.8	+10.7**	+19.9**	+17.8**	-2.9	-8.8**
Compound (c)	20	+1.3	-1.2	+7.2	+3.0	-4.2	-6.0
Compound (d)	20	+8.8*	+8.4**	+3.3	+7.3*	-3.7	-2.5
Compound (e)	20	-2.3	+6.6**	+10.9	+9.8*	-8.7*	-7.0**

t-test: *P < 0.05; **P < 0.01

Donovan Ex. 24 ('777 Patent) at cols. 5-6, line 7. Blood Glucose : Dose of each compound effective to reduce blood glucose or plasma triglyceride by 25% as compared to control. *Id.* at col. 4, lines 32-64. Toxicity: Dose of 100 mg/kg/day each compound administered daily for two weeks. The data represent percent increase or decrease from control (non-drug treated). *Id.* at col. 4, line 66 – col. 5, line 13.

SKB Hr'g Ex. SJ-2A; Ex. 24 ('777 Patent) at Table 1 (cols. 5-6); Jurs Decl. ¶ 36; Taylor Decl. ¶ 71. In the table, the results of blood glucose-lowering activity studies are reported as an "ED_{25}" value. This refers to the quantity, or dose, of the compound required to lower the mouse's or rat's blood glucose level by 25% and is

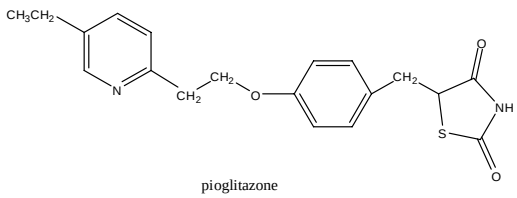
a measure of the potency of the compound. Lower ED_{25} values indicate greater potency. Taylor Decl. ¶ 70. For example, compound (b), with an ED_{25} value of 4, is ten times as potent as ciglitazone, with an ED_{25} value of 40. Only those toxicity values in the table which are followed by one or two asterisks are statistically significant. Ex. 24 ('777 Patent) at Table 1 (cols. 5-6); Szot Decl. ¶¶ 30-32.

The '777 Patent concludes that pioglitazone (compound (I)) "is superior to the compounds (a), (c), (d) and (e) and comparable to the compound (b) in hypoglycemic and hypolipidemic activities, while showing extremely low toxicity as compared with compounds (a), (b), (d) and (e). Such an effect as above caused by the introduction of an ethyl group is quite unexpected." Ex. 24 ('777 Patent) at col. 6, lines 1-07; Teva Rule 56.1 ¶ 127. Then, the '777 Patent concludes that "[t]herefore, compound (I) [pioglitazone] is of value as a therapeutic agent for Type II diabetes accompanied by obesity or hyperlipemia in mammals including man." Ex. 24 ('777 Patent) at col. 6, lines 11-60; Teva Rule 56.1 ¶ 133.

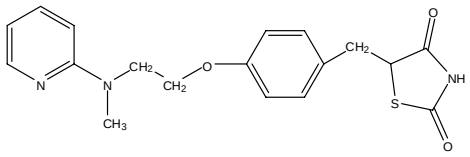
The methylpyridyl TZD identified as compound (b) in the '777 Patent is the same as compound 58 in Sohda II – one of only two compounds in Sohda II that contain a 2-pyridyl ring. Ex. 24 ('777 Patent) at Table 1 (cols. 5-6); Ex. 22 (Sohda II) at Table IV. Sohda II states that this compound was potent but "caused considerable increases in body weight and brown fat"; the '777 Patent similarly teaches that it was the most potent of the listed compounds, but it exhibited

statistically significant toxicities across all three toxicity parameters reported in the patent, causing increases in liver weight in female rats, increases in heart weight in male and female rats, and decreases in the number of erythrocytes in female rats. Ex. 22 (Sohda II) at p. 3589; Ex. 24 ('777 Patent) at Table 1 (cols. 5-6); Teva Rule 56.1 ¶¶ 135, 137; Ex. 52 (Kier Tr.) at 171:12-22.

Pioglitazone has an ethyl (CH_3CH_2) group located on the 5- position of the 2-pyridyl ring, while the 2-pyridyl ring in rosiglitazone is unsubstituted. Taylor Decl. ¶ 77. In addition, rosiglitazone has a methylamino (NCH_3) group next to the two methylene groups which pioglitazone lacks. *Id.*; Teva Rule 56.1 ¶ 147.



pioglitazone



rosiglitazone

B. Teva's Lipophilicity-Based Obviousness Theory

As discussed above, Teva has the burden of showing that a person of ordinary skill in the art in 1987-88 would have had a reason to modify a prior art compound in a particular manner in order to arrive at rosiglitazone. It also bears the burden of showing that such a person would have a reasonable expectation that rosiglitazone would be useful for treating Type 2 diabetes. *KSR*, 127 S. Ct. at 1741; *Takeda*, 2007 WL 1839698, at *5. These elements of Teva's case must be shown by clear and convincing evidence. *Takeda*, 2007 WL 1839698, at *3.

Teva's obviousness theory begins with the concept of lipophilicity. The

lipophilicity (or conversely, hydrophilicity) of an organic compound describes its tendency to partition between a lipid phase and an aqueous phase. Kier Decl. ¶ 13. If a compound is lipophilic, it will be attracted to lipids (or fats), as opposed to water; if a compound is hydrophilic, it will be attracted to water, rather than fats. Accordingly, a lipophilic compound placed into a vessel with a layer of water and a layer of fat will tend to distribute itself in the fat layer. Log P and Log D are numerical parameters that provide a measure of the lipophilic character of a compound. Kier Decl. ¶¶ 13-14. (Sometimes, the phrase "C Log P" or "C Log D" has been used, referring to "calculated" Log D or Log P. This is because, as discussed below, Log P or Log D may be calculated by a computer program on the basis of Log P values that have been experimentally determined for different moieties or fragments of compounds.) The higher the Log P or Log D value, the more lipophilic the compound. Jurs Decl. ¶ 11. While Log P and Log D are different, they are quantitatively related.[4] Here, for the TZD compounds

[4] When measuring Log P, the compound is assumed to be in its neutral form. However, some chemical compounds, such as acids and bases, contain groups that ionize in solution, meaning that they donate a proton (H^+) (resulting in a negatively charged compound) or accept a proton (resulting in a positively charged compound). The ionization constant, pKa, provides a measure of how readily a proton is donated. The extent of ionization depends on the strength of the acidic or basic group as well as the pH and the temperature of the solution. Log D takes into account the degree of ionization (pKa) of the compound and the pH of solution and can be calculated if both the Log P and pKa of a compound are known. Jurs Decl. ¶¶ 13-15; Kier Decl. ¶¶ 14-15. Log D and Log P are quantitatively related by a known equation: Log D = log P - log [1+antilog (pKa - pH)]. Kier Decl. ¶ 14.

containing a 2-pyridyl ring, the difference in Log P and Log D values is not significant. *See* Kier Decl. ¶ 66 (table listing Log P, pKa and Log D values). Ciglitazone and hydroxyciglitazone have the same Log P and Log D values. *Id.*

Lipophilicity provides information about how a drug will partition (*i.e.*, be distributed) in the body as between cell membranes (which are lipids) and intercellular and cellular fluids (which are aqueous). Kier Decl. ¶ 16; Teva Rule 56.1 ¶ 58. The parties agree that a person of ordinary skill in the art would have known, based on his general knowledge, that the lipophilicity of a compound influences it ability to be absorbed along the gastrointestinal tract into the bloodstream upon oral administration, and its distribution from the blood to the body's tissues. Kier Decl. ¶ 16; Jurs Decl. ¶ 18.

Dr. Kier testifies that, given a group of compounds having a known type of biological activity, optimizing lipophilicity would improve absorption, distribution and cell permeability of a novel compound and would therefore result in its increased bioavailability, which in turn would be expected to increase its relative potency. Kier Decl. ¶ 16.

Teva's lipophilicity-based obviousness theory then proceeds through a series of steps, as follows:

> 1) Based on the prior art, a person of ordinary skill in the art would have understood pioglitazone to be the "optimal compound" and would have selected pioglitazone as a "lead" in making a new drug to treat Type 2 diabetes. Teva Br. at pp. 7, 11.

2) The person of ordinary skill would have retained certain "key structural characteristics" of pioglitazone, namely the oxybenzyl-TZD moiety, a linker comprised of two methylene groups, and a 2-pyridyl "terminal fragment." Kier Decl. ¶ 59. (Dr. Kier does not suggest that a person of skill in the art would have retained the ethyl substituent on the 2-pyridyl ring, which the '777 Patent credits for pioglitazone's success.)

3) The skilled person would have correlated the lipophilicities of the "terminal fragments" (as Teva defines that term) of selected prior art compounds (including pioglitazone, ciglitazone, the hydroxyciglitazones disclosed in the '902 Patent, and the methylpyridyls disclosed in Table 1 of the '777 Patent) with the relative potencies of those compounds in order to derive an "optimal range" of Log D values within which he would have a reasonable expectation of finding compounds with good antidiabetic activity and low toxicity. Kier Decl. ¶¶ 67, 71-72.

4) Applying this approach in the manner described below, Dr. Kier arrives at an optimal Log D range of 1.2 - 1.8, which is framed at its bottom end (1.2) by the methylpyridyl compounds of the '777 Patent and at its top end (1.8) by the hydroxyciglitazone compounds disclosed in the '902 Patent. Kier Decl. ¶ 72.

5) The person of ordinary skill in the art would then create a new compound by modifying the 2-pyridyl terminal fragment in pioglitazone (to which the ethyl (CH_2CH_3) is attached in the 5 position) with a 2-pyridyl terminal fragment whose lipophilicity comes within the "optimal Log D range," with a reasonable expectation that the modified compound would have "equivalent or better potency as compared to pioglitazone, and therefore a similar or better margin of safety." Teva Br. at pp. 1, 10; Teva Rule 56.1 ¶ 35; Kier Decl. ¶¶ 73, 76, 78.

C. SKB's Criticisms of Teva's Theory of Obviousness

For summary judgment purposes, SKB does not dispute that the person of ordinary skill in the art at the time of rosiglitazone's invention might have selected pioglitazone as a lead compound or that such a person would have considered

lipophilicity as one tool in an effort to discover a novel drug to treat diabetes. Jurs Decl. ¶ 19.

Nevertheless, SKB argues that Dr. Kier's obviousness analysis is legally flawed for at least four reasons, each one of which is an independent ground for granting SKB's motion for summary judgment.

> 1.) Teva cannot show, and the prior art contradicts the conclusion, that a person of ordinary skill in the art would or could have used lipophilicity as a reliable way of accounting for differences in activity or potency of the prior art compounds.
>
> 2.) Teva cannot show a rational basis consistent with the prior art, for constructing the so-called optimal range of lipophilicity.
>
> 3.) Teva cannot show, and the prior art contradicts the conclusion, that a person of ordinary skill in the art could have used lipophilicity to form a reasonable expectation of successfully making a compound with low toxicity.
>
> 4.) Teva cannot show that in 1987-88, a person of ordinary skill would have concluded that the Log D value of rosiglitazone is even within the "optimal Log D range" hypothesized by Dr. Kier.

SKB Br. at p. 7.

1. Whether The Prior Art Showed A Predictable Relationship Between Lipophilicity and the Activity or Potency of a New TZD Compound

At the core of Dr. Kier's lipophilicity-based theory of invalidity is the assertion that there exists a meaningful relationship between the lipophilicities and potencies of prior art TZD compounds which would have given a person of ordinary skill in the art a reason to develop an "optimal range" of lipophilicities,

within which he would have a reasonable expectation about the activity or potency of new and untested TZD derivatives. Teva Opp. at p. 1; Kier Decl. at ¶¶ 43, 66-72. *See Takeda*, 2007 WL 1839698, at *5. SKB argues that there is no support for this assertion and to the contrary, it is contradicted by the record evidence and by Dr. Kier's deposition admissions. SKB Br. at pp. 24-25; SKB Reply at pp. 17-20.

a. The Alleged Absence of Logical Support for the Theory.

As an initial matter, SKB argues that, even accepting that lipophilicity was part of the general knowledge in the art, Dr. Kier's focus on lipophilicity as a guide for making a new TZD antidiabetic drug is illogical because, as a matter of basic science and general knowledge, it was understood that the bioavailability of the drug (which lipophilicity affects) is not the sole, or even key, determinant of a drug's activity. As SKB explained:

> a pharmaceutical compound is a complex, specific, 3-dimensional arrangement of atoms. The therapeutic effect of a drug compound depends on whether and to what extent it binds to specific binding site ("receptor") in a human cell, a process that is often analogized to whether a key (the compound) will fit into a lock (the receptor). That binding affinity is largely determined by the particular arrangement of atoms which determines the compound's size, shape, 3-dimensional configuration, electronic properties, chemical reactivity, and other characteristics relevant to receptor binding. Only drug molecules with the right shape, size and charge will fit into the binding sites of the receptor and "turn the lock." As a result, the therapeutic effect of a specific combination of atoms is unpredictable, especially in complex biological systems.

SKB Reply at pp. 5-6. *See also* SKB Br. at p. 23; Taylor Decl. at ¶¶ 26-29.

Teva does not dispute this basic scientific principle. Dr. Kier testified that it was general knowledge in the late 1980s that drug compounds produce their biological effects by binding to receptors; that a drug must bind to its receptor to have high potency; and that lipophilicity is only "a very minor aspect" of such binding:

> Q. It was known in 1987-88, was it not, that drugs produce their biological effects by binding with receptors themselves?
> A. This was general knowledge, yes.
>
> * * *
>
> Q. You would agree that Log D does not affect the ability of the molecule to bind to the active site receptor?
> A. That is the general presumption that is made, yes.
>
> * * *
>
> Q. In order for a compound to have high potency, there has to be binding between the [drug] molecule and the target active site receptor, correct?
> A. Correct.
>
> Q. And that will depend upon, in part, the steric properties of the portion of the molecule that is involved in binding to the active site receptor?
> A. That's one ingredient in the structure of the active site of the molecule, yes.
>
> Q. Others would include, for example, electronic properties?
> A. Yes.
>
> Q. And there are other factors as well?
> A. Yes.
>
> Q. But lipophilicity is not one of those factors?
> A. It's a very minor aspect, yes. Ex. 52 (Kier Tr.) at 64:19-22, 100:7-11, 100:24-101:17.

In light of these admissions, SKB argues, there is no sound basis for Dr. Kier's

conclusion that one skilled in the art would have assumed a correlation between lipophilicity and activity/potency for TZD compounds.

In addition, Dr. Kier relies on an article, written by SKB scientists ten years after the invention of rosiglitazone, that describes how the SKB scientists used lipophilicity at an early stage in their research program as a crude guide to trial and error modifications of molecules. Kier Decl. ¶ 29. The article -- although not prior art -- strongly supports SKB's arguments concerning the limitations of using lipophilicity as a guide to making a novel TZD. That article states that the experimental data showed no meaningful relationship between activity and lipophilicity for the tested compounds: "While the CLog *P* values of [three TZD compounds] are comparable, a 100-fold difference in potencies was observed. This suggests that, contrary to our original postulate, hydrophilicity[5] is ***not*** an important criterion for the enhanced potency of these compounds." Ex. 15 (Cantello 1) at p. 3979 (emphasis added). Thus, SKB's real life drug discovery program showed that TZD compounds with similar lipophilicities could have enormously different potency; *i.e.*, the scientists who actually considered lipophilicity found that there was not a useful correlation between activity/potency and lipophilicity for the TZD compounds they were investigating.

---

[5] As mentioned above, hydrophilicity refers to how "water loving" a compound is, and is the converse of "lipophilicity." A hydrophilic compound will have lower lipophilicity and a lower Log P value. Jurs Decl. ¶¶ 9, 11.

b. The Prior Art's Treatment of Lipophilicity.

Teva relies on Dr. Kier's opinions that (a) the activity (*i.e.*, receptor binding) of a TZD compound is principally provided by the "oxybenzyl TZD fragment," while the "terminal fragment" principally affects its bioavailability (*i.e.*, how much of the compound gets to the receptor site); (b) the prior art as a whole taught that the lipophilicity of the 2-pyridyl "terminal fragment" in pioglitazone and its structural analogues significantly influenced the potency of those compounds compared to ciglitazone; and therefore, (c) a person of ordinary skill in the art would have used the lipophilicities of the "terminal fragments" of TZD compounds with high potency as a guide to modifying pioglitazone's terminal fragment with the reasonable expectation that doing so would result in increased bioavailability and, therefore, higher potency. *See* Kier Decl. ¶¶ 20, 22, 44, 54, 58, 67. *See also* Teva Opp. at pp. 17-18; Teva Suppl. Br. at pp. 6-7.

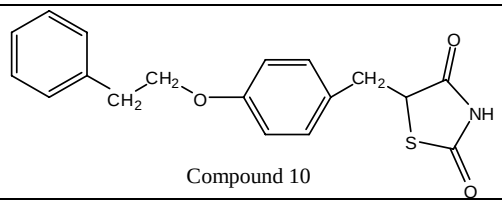
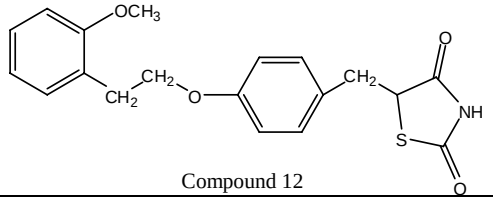
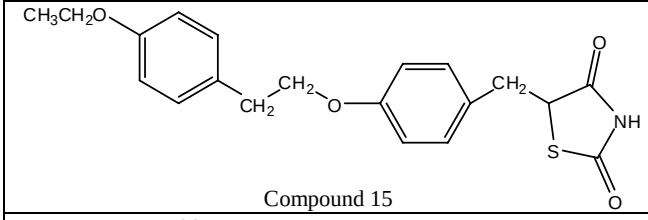
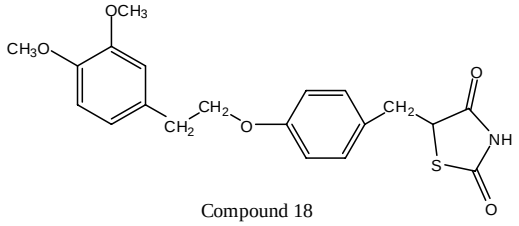
SKB contends that Dr. Kier's testimony cannot satisfy the "clear and convincing" standard in this case because: a) the very prior art relied on by Teva actually disproves the existence of a correlation between biological activity (or potency) and lipophilicity for these compounds; b) Dr. Kier has admitted that Sohda II, the '902 Patent, and the '777 Patent confirm there is no such correlation; and c) Dr. Kier never performed any statistical analysis for the prior art compounds that proved the contrary. 6/28/07 Hr'g Tr. p. 110-111; Ex. 52 (Kier Tr.) at 41:19-

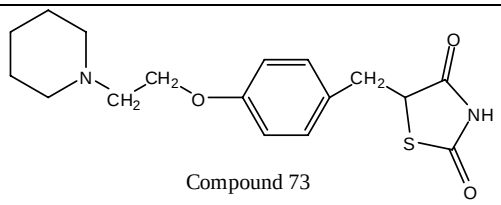
22, 163:25-164:20, 165:12-166:04, 167:20-169:05; Teva Rule 56.1 ¶¶ 70, 104, 122, 144, 158-159. SKB's arguments require the Court to review what the relevant prior art discloses about the relationship between lipophilicity and activity/potency, and Dr. Kier's statements concerning those disclosures.

Sohda II. Sohda II makes only one reference to lipophilicity (or hydrophilicity). Teva Rule 56.1 ¶ 104. As noted above, the article stated that the researchers at Takeda deliberately investigated "a series of compounds bearing less lipophilic groups" as terminal fragments. Ex. 22 (Sohda II) at p. 3589. However, the article concluded that although some of them showed potent activity, they also "caused considerable increases in body weight and brown fat weight." *Id.* Moreover, the two compounds with the "less lipophilic groups" that "especially" caused these problems, compounds 57 and 58, were the only two compounds that, like rosiglitazone, had a 2-pyridyl ring. *Id.* at Table IV. Of the three compounds that were called out as having "the most favorable profiles in terms of activity and toxicity," compounds 49 (ciglitazone), 47, and 59, only one (compound 59) was in the "series … bearing less lipophilic groups." *Id.* at 3589.

There is also no apparent relationship between activity and lipophilicity for the compounds that were most active, or selected as most favorable, in the Sohda II reference. Jurs Decl. ¶¶ 27-29. As explained above, compounds 49 (ciglitazone), 47 and 59, which were selected by Sohda II as exhibiting the most "favorable

profiles" in terms of activity and toxicity, have divergent "terminal fragment" structures, *i.e.*, a methylcyclohexyl group (ciglitazone), an unsubstituted cyclohexyl ring (compound 47), and a 3-pyridyl ring (compound 59), suggesting that no single physical parameter is important. Jurs Decl. ¶ 27. Examination of Sohda II's additional most active compounds, 10, 12, 15, 18 and 73, also reveals no discernable trends between lipophilicity and potency. *Id.* at ¶ 28. The Log D values for the terminal fragments of these compounds are 2.69, 2.56, 3.09, 2.30 and -1.38, a range that spans more than four logarithmic units, as shown below:

Sohda II Compound	**Hypoglycemic Activity / Hypolipidemic Activity**	**Log D**
 Compound 10	3 / 4	2.69
 Compound 12	3 / 4	2.56
 Compound 15	3 / 4	3.09
 Compound 18	3 / 4	2.30

 Compound 73	3 / 4	-1.38

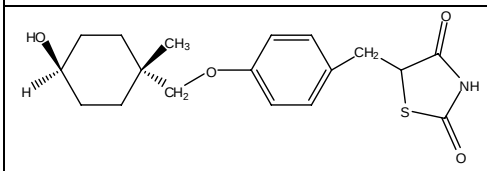
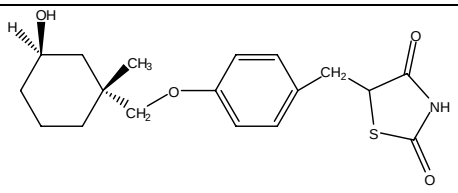
SKB Hr'g Ex. SJ-5; Jurs Decl. ¶ 28. At his deposition, Dr. Kier admitted that despite their high activity, he did not consider these five additional most active active compounds in Sohda II in his analysis:

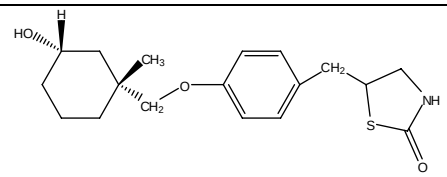
> Q: [Y]ou reached your conclusions as to what an optimal range of lipophilicity would be without knowing what the Log P values were of these five active compounds reported in Sohda II, correct?
> A: Yes, that's correct.
>
> Q: Does that suggest to you that there are compounds having a higher Log P that could also be active?
> A: Yes. There are always some compounds that might fall outside of the range and still have activity. Ex. 52 (Kier Tr.) at 188:9-21.

The '902 Patent. The '902 Patent never mentions lipophilicity (or hydrophilicity). Teva Rule 56.1 ¶ 122; Ex. 23 ('902 Patent). However, column 7 of the '902 Patent shows clearly that compounds with similar lipophilicities differ significantly in their hypoglycemic activities. Ex. 23 ('902 Patent) at col. 7, lines 1-22; Taylor Decl. ¶¶ 61-65; Jurs Decl. ¶¶ 31-34.

As explained above, compounds 6 and 7 differ only in the spatial orientation of the hydroxy group on the 3-position of the terminal methylcyclohexyl ring. Taylor Decl. at ¶ 65. There is no dispute that one skilled in the art would have understood that these compounds have very similar lipophilicities, and indeed, for

purposes of his analysis, Dr. Kier assumed all of the '902 compounds had the same Log P value. Kier Decl. ¶ 62; Ex. 52 (Kier Tr.) at 164:6-9; Teva Rule 56.1 ¶ 113. Nevertheless, these compounds exhibit markedly different hypoglycemic activities, showing 369% and 125% decreases in blood glucose lowering activity, respectively, as compared to ciglitazone. Ex. 23 ('902 Patent) at col. 7, lines 1-22; SKB Hr'g Exs. SJ-3 and SJ-3A; Taylor Decl. ¶¶ 63-64. Similarly, Compounds 2 and 6 differ only in that Compound 2 contains a hydroxy group on the 4-position of the terminal methylclyclohexyl ring while Compound 6 contains a hydroxy group on the 3-position. Taylor Decl. ¶ 65. As noted above, these compounds also have very similar lipophilicities. Yet, Compounds 2 and 6 have a large difference in their hypoglycemic activities, showing 118% and 369% decreases in blood glucose lowering activity, respectively, as compared to ciglitazone. *Id.*

'902 Patent Compound	**Activity**	**Log D**
 Compound 2	118	1.8
 Compound 6	369	1.8

 Compound 7	125	1.8

SKB Hr'g Exs. SJ-3 and SJ-3A; Jurs Decl. at ¶¶ 30-34; Taylor Decl. ¶ 65.

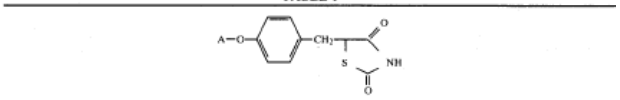
Again, Dr. Kier admitted at his deposition that lipophilicity does not account for the differences in hypoglycemic activity of the '902 Patent compounds:

> Q: Now if you look at these ['902 Patent hydroxyciglitazone] compounds and you compare compound two with compound six, compound six has three times the hypoglycemic activity, correct?
> A: Yes.
>
> Q: And yet they are both hydroxyciglitazone?
> A: Yes.
>
> Q: Would you agree that Log P does not account for that difference in activity?
> A: I would tend to agree with that. There's some other factor here.
>
> * * *
>
> Q: Could the difference in activity between [the hydroxyciglitazone] compounds two and six [of the '902 Patent] have been predicted using Log P?
> A: Probably not.
>
> Q: And Log D is not meaningful when we're talking about these compounds, correct?
> A: That's correct.
>
> Q: Could any of the differences in activity among the different forms of the hydroxyciglitazone [in the '902 Patent] have been predicted using lipophilicity?
> A: No, I don't think so.
>
> Q: The only way to know what these differences in activity are would

be to make the compounds and to test them in animals, correct?
A: Yes, sir. SKB Hr'g Ex. SJ-4; Ex. 52 (Kier Tr.) at 164:10-20, 165:12-166:04.

The '777 Patent. Like the '902 Patent, the '777 Patent never mentions lipophilicity (or hydrophilicity). Ex. 24 ('777 Patent); Teva Rule 56.1 ¶ 144. However, Table 1 of the '777 Patent shows clearly that the terminal fragment lipophilicities for the TZD compounds described therein do not explain or correlate with potency/activity. Ex. 52 (Kier Tr.) 167:20-169:05; Jurs Decl. ¶¶ 35-38; Taylor Decl. ¶ 79.

TABLE 1



Compound A	Blood Glucose (ED_{25})	TG(ED_{25})		Two-weeks toxicity (rat, %)					
				Liver weight		Heart weight		number of erythrocyte	
	mouse	mouse	rat	♂	♀	♂	♀	♂	♀
(I)	6	6	3	−0.7	−3.5	+0.9	−3.9	−3.4	−0.7
(a) (ciglitazone)	40	40	70	+6.6*	+10.8*	+13.4*	+4.0	+3.5	−0.2
(b)	4	3	5	+3.8	+10.7**	+19.9**	+17.8**	−2.9	−8.8**
(c)	20	20	—	+1.3	−1.2	+7.2	+3.0	−4.2	−6.0
(d)	20	20	—	+8.8*	+8.4**	+3.3	+7.3*	−3.7	−2.5
(e)	20	20	—	−2.3	+6.6**	+10.9	+9.8*	−8.7*	−7.0**

t-test: *P < 0.05; **P < 0.01

Ex. 24 ('777 Patent) at cols. 5-6; SKB Hr'g Exs. SJ-2A and SJ-2. Specifically, there is no dispute that one skilled in the art would understand that the lipophilicities of the methylpyridyl TZDs in Table 1, *i.e.*, compounds (b) – (e), are very similar, and yet compound (b) is five times more potent than compounds (c),

(d) and (e), a difference too large to be explained by the small differences in lipophilicity. Jurs Decl. at ¶¶ 35-38; Ex. 52 (Kier Tr.) at 167:20-169:05. Moreover, on its face, the '777 Patent credits the ethyl group in pioglitazone, not the lipophilicity of the terminal fragment, for the observed high activity of pioglitazone:

> As is apparent from the experimental results given in Table 1, Compound (I) of this invention is superior to compounds (a), (c), (d) and (e) and comparable to the compound (b) in hypoglycemic and hypolipidemic activities, while showing extremely low toxicity as compared to compounds (a), (b), (d) and (e). ***Such an effect as above caused by the introduction of an ethyl group is quite unexpected.***

Ex. 24 ('777 Patent) at col. 5, line 68 – col. 6, line 7 (emphasis added).

Dr. Kier admitted that the differences in potency of the '777 methylpyridyl compounds cannot be explained by lipophilicity, and that one could not have predicted these potency differences using only Log D:

> Q: The difference in potency [of the '777 Patent compounds B and C] cannot be explained by lipophilicity, can it?
> A: No.
>
> * * *
>
> Q: And would you agree that one could not have predicted this difference – one could not have reasonably predicted this difference in potency based simply on Log D?
> A: Probably not.
>
> Q: That in order to determine that there is this difference in potency, it would have been necessary to make the compound and to test it experimentally in animals as was done by researchers at Takeda?
> A: Yes. SKB Hr'g Ex. SJ-4; Ex. 52 (Kier Tr.) at 168:03-05, 168:18-169:05.

Dr. Kier admitted that the effects of pioglitazone were caused by the introduction of the ethyl group, and that the '777 taught that the ethyl group was "beneficial":

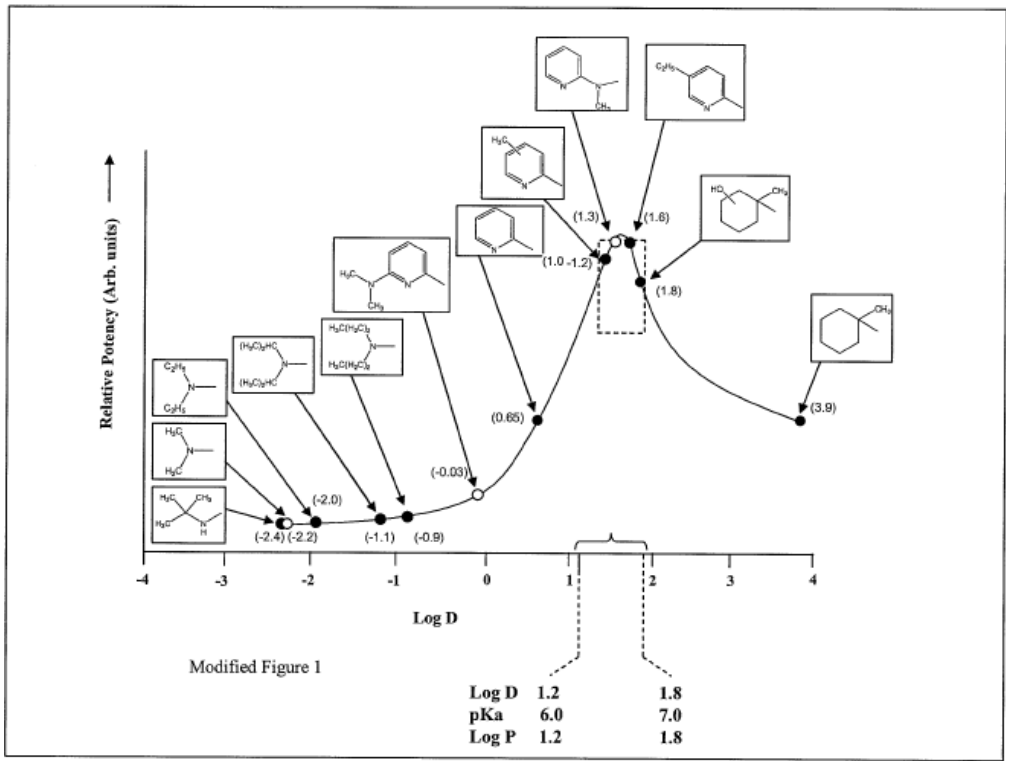
> Q: Was it reasonable for the ['777 Patent] inventors to have concluded that the effects [of pioglitazone] were caused by the introduction of an ethyl group?
> A: I think so.
>
> Q: Now is there any teaching in the '777 Patent that the ethyl group is unnecessary to the benefits that are attributed to pioglitazone?
> * * *
> A: -- unnecessary. Well, I'm not familiar with that in the '777.
>
> Q: You would agree, would you not, that the '777 Patent teaches that the ethyl group is beneficial?
> A: Yes. Ex. 52 (Kier Tr.) at 180:18-181:12.

Based on this review of the relevant prior art references, as well as Dr. Kier's admissions, the Court concludes that the prior art did not provide a reason for a person of ordinary skill to use the lipophilicities of the prior art compounds in order to construct an "optimal range" of lipophilicities within which he would have a reasonable expectation of finding a compound useful as an antidiabetic agent. Rather, the prior art showed that compounds with very similar lipophilicities could unpredictably have very different activity/potency, depending on very minor structural differences.

c. Dr. Kier's Figure 1.

Teva claims that even if the prior art as a whole does not show a relationship

between lipophilicity and potency for TZD compounds generally, Dr. Kier's analysis appropriately focused on the relative potencies and lipophilicities of a "small subset" of six structurally analogous, "potent compounds, namely pioglitazone and its 2-(methylpyridyl) analogues" – *i.e.*, the compounds that appear in Table 1 of the '777 Patent – as well as the hydroxyciglitazones disclosed in the '902 Patent. Kier Decl. ¶ 62; Teva Rule 56.1 ¶¶ 15-59. Dr. Kier then contrasted the potencies and lipophilicities of these compounds with other prior art compounds having lower activity. Teva Rule 56.1 ¶¶ 158-159; Kier Decl. at ¶ 72; Ex. 57 (Kier Tr.) at 181:20-184:19. The result is Dr. Kier's Figure 1 in which he derived an "optimal range" of lipophilicities for the terminal fragments of TZD compounds. Figure 1 is shown below:



Dr. Kier testified that Figure 1 was hand-drawn to show a curvilinear relationship between lipophilicity (Log D), on the y-axis, and relative potency, on the x-axis. Ex. 57 (Kier Tr.) at 222:10-17. That is, pioglitazone is shown on the chart as having the highest potency of all the reported compounds, and its "terminal fragment" is shown as having a Log D value of 1.6. Relative potency of the other prior art compounds in the chart drops off as the Log D of the terminal fragments of those other compounds falls below 1.6 or rises above 1.6. Thus, Figure 1 suggests that the terminal fragment of pioglitazone has an "optimal" Log D; as discussed above, Dr. Kier suggests that one skilled in the art would conclude what this chart suggests -- that pioglitazone owes its superior potency (as compared to the prior art compounds) to its optimal lipophilicity and not, as the '777 Patent expressly states, to the unique structure of an ethyl group attached to a 2-pyridyl ring at the 5 position. Teva Rule 56.1 ¶ 128; Kier Decl. ¶ 68. Therefore, Dr. Kier argues, one skilled in the art would attempt to find a TZD compound with a terminal fragment that has a Log D value within a very narrow range (1.2 - 1.8), spanning about 0.6 Log D units around the Log D value of the terminal fragment of pioglitazone. Kier Decl. ¶¶ 67, 72.

At oral argument, when SKB pointed out that "Relative Potency" axis in Figure 1 is stated in "arb. units," *i.e.*, arbitrary units, Teva's counsel explained that Sohda II, the '902 Patent, and the '777 Patent all present the hyperglycemic

activities of compounds in different ways, and as a result, Dr. Kier "eye balled" the data to construct the curve in Figure 1. *See* 6/28/07 Hr'g Tr. at 88:06-09; 100:02; 100:17-21; Ex. 57 (Kier Tr.) at 41:19-42:02. In doing so, however, Dr. Kier has admittedly made some omissions. For example, although Figure 1 shows a single data point for all hydroxyciglitazones (at a Log D of 1.8), the '902 Patent in fact shows that the activities of those compounds varied more than three-fold, depending on where the hydroxy (OH) is attached to the methylcyclohexyl ring, a factor which would not have a material effect on lipophilicity. Ex. 23 ('902 Patent) at col. 7, lines 1-22; Ex. 52 (Kier Tr.) at 163:25-164:69; SKB Hr'g Ex. SJ-4; 6/28/07 Hr'g Tr. at 85:13-86:25. Thus, although all of the hydroxyciglitazones have about the same lipophilicity, they clearly do not all have the same "Relative Potency (arb. units)"; yet, Figure 1 shows a single "Relative Potency (arb. units)" for all of them. SKB Hr'g Exs. SJ-3 and SJ-3A; Kier Decl. ¶ 72.

Similarly, Figure 1 has a single "Relative Potency (arb. units)" data point for the methylpyridyls disclosed in the '777 Patent, even though Table 1 of that patent shows that compound (b) is five times more potent than compounds (c), (d), and (e). Ex. 24 ('777 Patent) at Table 1 (cols. 5-6); Kier Decl. ¶ 72; SKB Hr'g Exs. SJ-2 and SJ-2A; 6/28/07 Hr'g Tr. at 80:16-85:12. In addition, Figure 1 shows rosiglitazone and pioglitazone as having virtually the same "Relative Potency (arb. units)" when other sources indisputably show that rosiglitazone is significantly

more potent than pioglitazone. Ex. 16 (Cantello 2) at p. 1182.

Figure 1 also excludes the most active compounds in Sohda II which have terminal fragments with lipophilicities above or below Dr. Kier's "optimal range." Kier Decl. ¶ 72; Ex. 57 (Kier Tr.) at 185:06-22, 188:09-14. As discussed above, among the most active compounds in Sohda II were compounds 10, 12, 15, 18, and 73 – *i.e.*, these compounds were all at least as active as ciglitazone and so would have a "Relative Potency (arb. units)" on Figure 1 equal to or above that of ciglitazone. Ex. 22 (Sohda II) at Tables I and IV; Jurs Decl. ¶ 28. Further, as shown above, the terminal fragment lipophilicity of each of these compounds falls either above (compounds 10, 12, 15, and 18) or below (compound 73) the "optimal range" identified in Figure 1. Kier Decl. ¶ 72; Jurs Decl. ¶ 28. Dr. Kier did not show this data in Figure 1. Kier Decl. ¶ 72; Ex. 57 (Kier Tr.) at 185:06-22, 188:09-14. Indeed, if the terminal fragment lipophilicities of all of these most active compounds in Sohda II, all of the methylpyridyls in the '777 Patent, and all of the hydroxyciglitazones in the '905 Patent were included in Figure 1, it clearly would look more like a scatter shot of data points instead of the neat curvilinear relationships between Log D and "Relative Potency (arb. units)" which is depicted.

To justify the fact that Figure 1 is based on relatively few compounds, Teva cites Dr. Kier's opinion that it is appropriate to consider only compounds that share "key structural characteristics" with pioglitazone, most importantly (a) a linker

comprised of two methylene groups and (b) a 2-pyridyl terminal fragment. Teva Opp. at pp. 2-3; Kier Decl. ¶¶ 59, 61, 63. Teva, however, has provided very little explanation of how or why Dr. Kier has concluded that these two features are "key structural characteristics" when the '777 Patent says, on its face, that it is the ethyl, substituted at the 5-position on a 2-pyridyl ring, that is responsible for its high activity. Ex. 24 ("777 Patent) at col. 5, line 68-col. 6, line 07. To the contrary, Dr. Kier's conclusions are inconsistent with his own admissions that the '777 patent inventors reasonably concluded the ethyl group was responsible for pioglitazone's effects, and that the '777 patent teaches that the ethyl group is beneficial. Ex. 52 (Kier Tr.) at 180:18-181:12.

Nor has Teva explained why the skilled person would have been motivated to limit a lipophilicity study to TZDs with a 2-pyridyl terminal fragment when both Sohda II and Table 1 of the '777 Patent suggested that 2-pyridyl TZDs were likely to be toxic. Ex. 22 (Sohda II) at p. 3589; Ex. 24 ('777 Patent) at Table 1 (cols. 5-6). And in any event, Figure 1 also includes ciglitazone and hydroxyciglitazones which do not have 2-pyridyl terminal fragments, indicating that Dr. Kier's study was not limited to compounds with a 2-pyridyl terminal fragment.

In sum, the relevant prior art did not suggest a relationship between lipophilicity and activity, principally because compounds with similar lipophilicities had been shown to have very different activities. Dr. Kier's Figure 1

does not avoid that conclusion. Because a predictable relation between lipophilicity and potency lies at the heart of Teva's lipophilicity-based obviousness defense, and because Teva cannot show by clear and convincing evidence that one skilled in the art would conclude that such a predictable relationship existed for TZD compounds, Teva's obviousness defense fails.

2. Whether The Prior Art Would Lead One To Dr. Kier's "Optimal Range" of Lipophilicities

SKB also argues that Teva cannot show a basis in the prior art or in logic for constructing the so-called "optimal range" of lipophilicity on which Dr. Kier's theory turns. To the contrary, Dr. Kier's "optimal range" is framed by compounds which the prior art shows did not have practical utility as antidiabetic agents. Accordingly, Teva cannot show by clear and convincing evidence that a person skilled in the art would have a reason to frame a lipophilicity range using these compounds.

a. Dr. Kier's Basis for Selecting the Upper and Lower Limits of the "Optimal Range."

Dr. Kier used Figure 1 to conclude that at the time of the invention in 1987-1988, a person of ordinary skill in the art would have limited his search for a novel TZD to treat Type 2 diabetes to TZDs with terminal fragments that had a Log D value in the range of 1.2 to 1.8, values which reflect the lipophilicities of the prior art methylpyridyls and hydroxyciglitazones, respectively. Kier Decl. ¶¶ 67, 72, 73.

However, in Teva's original Paragraph IV notice letter to SKB, in which it was required by statute to explain the basis for its contention that the '953 Patent was invalid, and in its interrogatory answers in this case, Teva chose different compounds to frame an "optimal" lipophilicity range, which led to a Log D range of 0.65 to 1.69. Ex. 6 (Avandia® Para. IV Letter) at 5; Ex. 7 (Avandamet® Para. IV Letter) at 6. Teva's changed initial position substantially undercuts its core obviousness argument. It is difficult to reconcile Dr. Kier's view that one skilled in the art in 1987-88 would have been led, by the prior art and general knowledge, to his "optimal range" when Teva, in a letter signed by one of its scientists, arrived at a different "optimal range" based on different compounds. *See Takeda*, 417 F. Supp. 2d at 366-67, 372 n.37, 387.

In any event, because Teva must show by clear and convincing evidence that a person of ordinary skill would reasonably expect compounds falling within its range to have high potency and low toxicity -- *i.e.*, that they could be used to treat diabetes -- it follows that Teva must show, at the very least, that the person of skill in the art would have reasonably expected the methylpyridyl and hydroxyciglitazone compounds framing its range to have those beneficial characteristics. But as Teva has admitted (Teva Rule 56.1 ¶ 121, 152-157), the '777 Patent explicitly taught that these other compounds could not be put to practical use: "Those compounds, however, have not yet been put to practical use.

As the reasons, (1) insufficient activities or/and (2) serious toxicities may be mentioned." Ex. 24 ('777 Patent) at col. 1, lines 18-27.

Not only did the '777 Patent state generally that the compounds which Dr. Kier used to frame the bottom and top of his "optimal range" were not put to practical use; the prior art confirmed this specifically. Thus, Dr. Kier framed the bottom of his "optimal range" using the methylpyridyl TZD compounds from Table 1 of the '777 Patent because they showed high potency. In point of fact, however, the '777 Patent showed that a methylpyridyl TZD may or may not have high potency and often exhibits significant toxicity, depending on where the methyl group is attached to the 2-pyridyl ring. Ex. 24 ('777 Patent) at Table 1 (cols. 5-6). Thus, Compound (b) in Table 1 showed the greatest potency, but also exhibited statistically significant toxicities across all three parameters presented, *i.e.*, it caused increases in liver weight in female rats, increases in heart weight in male and female rats, and decreases in the number of erythrocytes in female rats. Ex. 24 ('777 Patent) at Table 1 (cols. 5-6); Szot Decl. ¶ 31. In fact, compound (b) in the '777 Patent is the same as compound 58 in Sohda II, and the Sohda II article criticized it because of its undesirable side effects. Ex. 22 (Sohda II) at p. 3589 and Table IV; Ex. 24 ('777 Patent) at Table 1 (cols. 5-6); Szot Decl. ¶¶ 23-24. This data would not lead one of skill in the art to consider this compound. Szot Decl. ¶¶ 24-25; Taylor Decl. ¶ 57. That is precisely what the district court in *Takeda* found:

"[O]ne skilled in the art would have done an initial screening of compound (b) for toxicity and concluded that its toxicity made it an extremely poor candidate for modification." *Takeda*, 417 F. Supp. 2d at 380. As for the other methylpyridyls TZDs in the '777 Patent, Compounds (d) and (e) also showed statistically significant signs of toxicity, while compounds (c), (d), and (e) were all significantly less potent than pioglitazone. Ex. 24 ('777 Patent) at Table 1 (cols. 5-6); Szot Decl. ¶¶ 32, 34. In short, the prior art would not have suggested that the methylpyridyl TZDs could be used to treat diabetes.

The upper end of Dr. Kier's "optimal range" suffers from the same problem. Dr. Kier chose the hydroxyciglitazones to frame the upper end of his range, again allegedly because of their supposed high activity. However, the '902 Patent showed that the activity of the hydroxyciglitazones varied widely depending on the position of the attachment of the hydroxy group to the methylcyclohexyl ring and its three-dimensional orientation. Ex. 23 ('902 Patent) at col. 7, lines 1-22; SKB Exhibits SJ-3; SJ-3A. And, while one of the hydroxyciglitazones was particularly active, Takeda had told the world in the '777 Patent that the hydroxyciglitazones were not of "practical use" because of insufficient activity and/or "serious toxicities," logically suggesting that the highly potent hydroxyciglitazone showed "serious toxicity." Ex. 24 ('777 Patent) at col. 1, lines 18-28.

In sum, the Court concludes that when the prior art is considered as a whole,

the construction of Figure 1 "lack[s] logical continuity," *Advanced Tech Materials*, 2007 WL 1158103, at *2, and can therefore be disregarded. Moreover, the prior art contradicts the conclusion that a person of skill in the art would have framed a range of "optimal" lipophilicities with the lipophilicities of the methylpyridyls and the hydroxyciglitazones because the prior art clearly stated and demonstrated that they could not be put to "practical use" to treat Type 2 diabetes due to toxicity and/or potency concerns.

In the absence of a reason for a person of skill in the art to construct Dr. Kier's "optimal range" of lipophilicities, Teva's obviousness defense fails.

3. Whether Using Relative Lipophilicities Would Have Led to a Reasonable Expectation of Low Toxicity

SKB also argues that Teva cannot show by clear and convincing evidence that a person of ordinary skill in the art would have used lipophilicity to form a reasonable expectation that a new TZD would have low toxicity. SKB Br. at pp. 31-32; SKB Reply at p. 24. SKB contends that this constitutes a failure of proof with regard to Teva's obviousness defense. *See Celotex*, 477 U.S. at 322-23; *Ortho-McNeil Pharm*, 2007 WL 432792, at *7; *Eisai*, 2006 WL 2872615, at *3.

As discussed above, Teva must show that one skilled in the art would have had a reasonable expectation of success in making a drug that would be useful in treating diabetes. Numerous courts evaluating a claim that a patent on a drug compound is obvious have ruled that a "reasonable expectation of success"

includes an expectation that the drug will lack toxicity. *See Yamanouchi*, 231 F.3d at 1345 (success was "finding a compound that had high activity, few side effects, and lacked toxicity"); *Takeda*, 417 F. Supp. 2d at 372 (success was "a non-toxic, effective treatment for diabetes"); *Eli Lilly*, 364 F. Supp. 2d at 905 (success was development of "a safe, effective, atypical antipsychotic drug"). Thus, Teva must show that a person of skill in the art would have had a reasonable expectation that rosiglitazone lacked toxicity/had an acceptable margin of safety.

Indeed, Teva itself repeatedly defined "reasonable expectation of success" in terms of whether one skilled in the art, making modifications to the prior art, would have had a reasonable expectation of producing "an effective antidiabetic agent." *See, e.g.*, Teva Opp. at pp. 1, 3-4, 6, 10, 12, 18, 20. Dr. Kier also agreed that a broad margin of safety is a necessary characteristic of an effective antidiabetic agent:

> Q: Do you agree that it was known by 1987-88 that a combination of high potency [and] a broad margin of safety was important for a TZD compound to be utilizable as an antidiabetic drug?
>
> * * *
>
> A: I think this was accepted as a criteria. Ex. 52 (Kier Tr.) at 16:21-17:06.

Both Teva and Dr. Kier also admitted that in the late 1980s, toxicity was a critical factor why drug compounds failed. Teva Rule 56.1 ¶ 57; Ex. 52 (Kier Tr.) at 126:20-127:03. Therefore, the Court concludes that whether a person of ordinary skill in the art would have been able to use lipophilicity to make a compound that

lacked toxicity/had an acceptable margin of safety is an essential element of Teva's lipophilicity-based theory of obviousness.

Teva asserts that there is a factual dispute on this issue, citing Dr. Kier's opinion that a person of ordinary skill in the art would have had a reasonable expectation that modifying pioglitazone to maintain the lipophilicity of the terminal fragment within his optimal range would produce a compound with "high activity and correspondingly sufficient margin of safety to make it appropriate for pharmaceutical usage." Teva Opp. at pp. 3-4, 21-23; *see also* Kier Decl. ¶ 68; Teva Supp. Br. at pp. 2, 8 n. 3.

This assertion is not supported by the record. Dr. Kier admitted that he did not consider toxicity in forming his optimal lipophilicity range.

> Q. Did you correlate toxicity with lipophilicity in your work in this case?
> A. No.
>
> ***
>
> Q. I take it you are not going to be opining in this case that there is an optimal range of lipophilicity with respect to avoiding toxicity in TZD compounds?
> A. Let's see. You're asking me if I have or am looking for an optimum lipophilicity to minimize toxicity. No. No. Ex. 52 (Kier Tr.) at 124:24-125:01, 125:14-20.

Furthermore, Teva has admitted that no prior art publication showed a correlation between lipophilicity and the absence of toxicity for the prior art compounds. Teva Rule 56.1 ¶¶ 70, 104, 122, 144. Teva has also admitted that Dr. Kier's lipophilicity range has no predictive value with regard to toxicity. Teva Rule 56.1

¶ 173; Ex. 52 (Kier Tr.) at 125:14-20.

In addition, Dr. Kier's assertion is contradicted by the prior art. In Table 1, compound (b) (the 6-methyl-2-pyridyl compound) is the most potent compound listed, but it exhibited statistically significant toxicities across all three parameters presented. Ex. 24 ('777 Patent) at Table 1, columns 5-6; Szot Decl. at ¶ 31. Teva admits that these changes associated with compound (b) were statistically significant and undesirable.[6] Teva 56.1 ¶ 135-137. Dr. Kier made the same admission at his deposition:

> Q. [I]f we look down at [the '777 Patent] compound B it reports a liver weight gain in male mice of 10.7 percent and a P value of less than .01. You would agree that that is undesirable?
> A. It's undesirable at that [dose], yes.
>
> Q. The heart weight gain that is reported for compound B, you would

[6] Teva also argues that because the '777 Patent compounds were not administered at their effective doses, a person of ordinary skill in the art would not "necessarily" have considered compound (b) to be toxic at its effective dose. Kier Decl. ¶ 84; Teva Suppl. Br. at 20. According to Dr. Kier, "the mere fact that there may be some physiological change other than the desired pharmacological activity at a substantially higher dose does not necessarily mean that a compound cannot be developed as a pharmaceutical product." Kier Decl. ¶ 82. However, Dr. Kier admitted that he is not a toxicologist, that he had never performed or designed a toxicity study, and that he has had no experience establishing dosages used in toxicity studies. Ex. 57 (Kier Tr.) at 20:9-13, 21:10-22:6. Therefore, Dr. Kier's opinions about toxicity should be discounted, if they are credited at all. More important, Dr. Kier's testimony that one would not "necessarily" conclude that compound (b) could not be "developed as a pharmacological product" is far from clear and convincing evidence that a person of ordinary skill in the art would have had a reasonable expectation that a novel TZD compound would have sufficiently low toxicity that it could be used as a drug and does not satisfy Teva's burden of proof.

agree is undesirable as well, correct?
A. Yes, at that weight and over that period of time, right. Ex. 52 (Kier Tr.) at 171:12-22.

Dr. Kier also admitted that increasing bioavailability – which is the stated reason for the optimal lipophilicity range – could sometimes make a compound more toxic:

Q: Now when you increase the bioavailability of a compound by altering its lipophilicity, does that sometimes make the compound more toxic?
A: It's possible that it could, yes.

Q: That's because?
A: Depending on where it ended up.

Q: It might have more availability at the wrong target receptor?
A: Exactly. Ex. 52 (Kier Tr.) at 130:10-20.

Based upon these admissions, the Court holds that Dr. Kier's conclusory opinions lack factual support in the record and are directly contradicted by the very prior art on which Teva relies. *Ashland*, 776 F.2d at 292. Accordingly, Teva cannot prove by clear and convincing evidence that the person of ordinary skill would have had a reasonable expectation that new TZD compounds within Dr. Kier's lipophilicity range would have lacked toxicity and/or would have an acceptable margin of safety.

4. Whether in 1987-88, One Skilled in the Art Would Have Concluded That Rosiglitazone Falls Within Dr. Kier's Optimal Lipophilicity Range of 1.2 to 1.8

As its final argument, SKB contends that even if the Court accepts that one

skilled in the art in 1987-88 would have constructed a narrow range of lipophilicities of certain select TZDs with a reasonable expectation that TZDs with lipophilicities within the range would be useful as antidiabetic agents, and even if the Court accepts that Dr. Kier correctly framed such a range, nonetheless, at the time of rosiglitazone's invention, a person of skill in the art would not have concluded that rosiglitazone came within Dr. Kier's optimal lipophilicity range. SKB Br. at pp. 26-31; SKB Reply at pp. 11-17. Accordingly, Dr. Kier's lipophilicity-based theory of obviousness fails because even following the theory, one skilled in the art would not have arrived at rosiglitazone.

Before turning to the parties' respective arguments, it is helpful to explain the "fragment method" that Dr. Kier used to determine his optimal Log D lipophilicity range of 1.2 to 1.8.

a. The "Fragment Method" for Determining Lipophilicity.

The parties agree that "all portions of a compound contribute to its overall lipophilicity." Teva Rule 56.1 ¶64; Ex. 52 (Kier Tr.) at p. 100:12-15. Therefore, all atoms in a compound should be considered when determining its lipophilicity. At the time that rosiglitazone was invented, however, the Log P for the TZD moiety was not available. *See* Motion to Strike Ex. F (Kier Tr.) at 82:11-24[7]; Ex.

[7] "Motion to Strike Ex. __" refers to Exhibits attached to the Declaration of Bindu Donovan in Support of SKB's Motion to Strike the Supplemental Declaration of Dr. Lemont Kier and to Preclude Teva from Relying upon Dr. Kier's Supplemental

16 (Cantello 2) p. 1184 n. 13 ("CLog P values were calculated in the MedChem program which was not parameterized for the 2, 4-thiazolidinedione moiety"). Thus, it was not possible for one skilled in the art at the time of the invention in 1987-88 to calculate the Log P or Log D of an entire TZD molecule. Motion to Strike Ex. F (Kier Tr.) at 82:11-24

It is also undisputed, however, that a person of ordinary skill in the art would have known that the ***relative*** lipophilicities of TZD compounds can still be meaningfully compared by comparing the lipophilicities of fragments of the molecules, so long as the contributions to overall molecular lipophilicity made by the remainder portions are essentially the same for all of the molecules. Kier Decl. ¶ 62.

For these reasons, Dr. Kier determined his optimal lipophilicity range based not on the lipophilicities of the entire TZD molecules in the prior art, but only of the left side "terminal fragments":

> Q: [F]or the TZD molecules you used the fragment system?
> A: Yes.
>
> Q: I take it you did not have a Log P value of the TZD oxy benzyl portion of the molecule, is that right?
> A: That's correct, yes.
>
> Q: And for that reason you tried to determine relative Log P values of different molecules by focusing on the left side of the molecule?
> A: Yes. Motion to Strike Ex. F (Kier Tr.) at 82:11-24.

Declaration on Summary Judgment or at Trial.

For summary judgment purposes, SKB agrees that such a "fragment method" is scientifically valid, but only if the contribution to overall lipophilicity of the "remainder fragments" is virtually the same for all of the molecules that are being compared. Dr. Kier agreed to this point in his declaration:

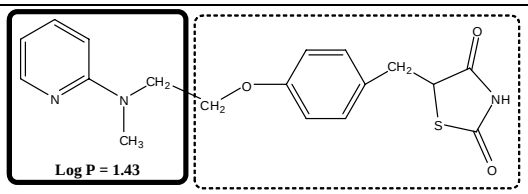
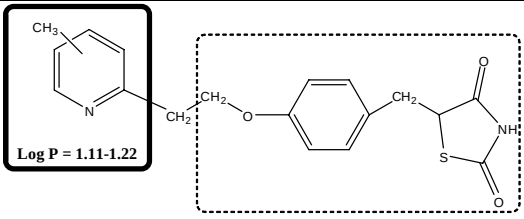
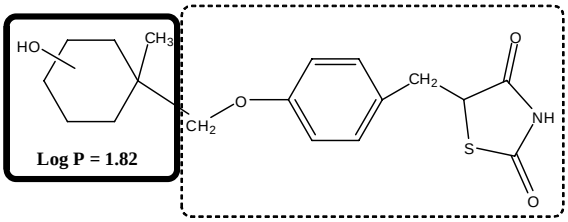
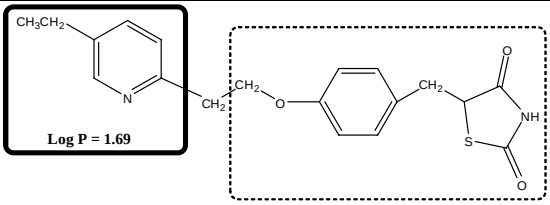
> [A] person of ordinary skill in the art would have known that the relative lipophilicities of ciglitazone, hydroxyciglitazone, pioglitazone, and pioglitazone analogue compounds having an unsubstituted 2-pyridyl and 2-(methylpyridyl) terminal fragment could be compared on the basis of the terminal fragment contribution to the lipophilicity (Log *P*) in those molecules, because one would assume that the active fragment and the linker group [i.e., the remainder portions of the molecule] make a ***virtually identical contribution*** to the overall lipophilicity in each of these molecules.

Kier Decl. at ¶ 62 (emphasis added).

One skilled in the art would understand that the remainder portions of the TZD molecules that are used to derive the lipophilicities shown in Dr. Kier's Figure 1 would "make a virtually identical contribution to the overall lipophilicity in each of these molecules" if either (a) the remainder portions were in fact identical; or (b) it was known at the time of rosiglitazone's invention that nonidentical remainder portions make a "virtually identical contribution to overall lipophilicity." Kier Decl. ¶ 62; Jurs Decl. ¶¶ 42-46. SKB argues that Teva has failed to show by clear and convincing evidence that either circumstance is true.

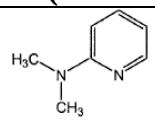
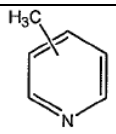
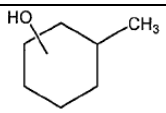
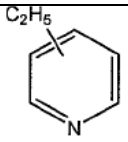
Dr. Kier's "optimal lipophilicity range" in Figure 1 is framed at the bottom end (Log D = 1.2) by the methylpyridyl TZDs, and at the top end (Log D = 1.8) by

the hydroxyciglitazones. Kier Decl. ¶¶ 67, 72. The lipophilicity reported by Dr. Kier for the rosiglitazone terminal fragment is 1.43, within Dr. Kier's calculated range. *Id.* at ¶ 74. However, the following chart illustrates the specific terminal fragments that Dr. Kier considered and the Log P values associated with them. Jurs Decl. ¶ 44; Ex. 58 (Kier Dep. Ex. 15). The chart shows that Dr. Kier did not keep the remainder portions identical:

Compound	**Structure of Compound Showing Terminal Fragment Used By Dr. Kier (Bold Box) And Remainder Portion of Molecule (Dotted Line)**
rosiglitazone	
methylpyridyl TZDs	
hydroxyciglitazones	
pioglitazone	

When the specific terminal fragments used by Dr. Kier and their associated

Log P or Log D values are examined, it is clear that Dr. Kier's fragment method treated each of the left-side terminal fragments as a separate, complete compound for which a Log P value was determined. Kier Decl. ¶¶ 62, 66, 74; Motion to Strike Ex. D (2/9/07 Letter from Gill to Beck) and Ex E (2/14/07 Letters from Gill to Beck) (collectively, "Motion to Strike Exs. D and E (Gill Letters)") This is clear from the chart in Dr. Kier's Declaration ¶ 62 and the drawing in Dr. Kier's Declaration ¶ 74, which show the terminal fragments as complete compounds and report the Log P values associated with those compounds, as shown below:

TZD Compound	**Compound Used by Dr. Kier to Compute Log P (*See* Kier Decl. ¶¶ 62, 66, 74; Motion to Strike Exs. D and E (Gill Letters))**	**Log P Reported By Dr. Kier (*See* Kier Decl. ¶¶ 62, 74)**
Rosiglitazone		1.43
methylpyridyl TZDs		1.11-1.22
Hydroxyciglitazones		1.82
Pioglitazone		1.69

b. Teva Has Admitted That The Remainder Portions of the TZDs Used to Construct Figure 1 Are Not Identical.

It is undisputed that in the case of rosiglitazone and the hydroxyciglitazone

compounds, Dr. Kier accounted for all of the atoms in the compound by assuming that the right side remainder portion of the compound included a single methylene group to the left of the oxybenzyl group. Kier Decl. ¶ 62; Jurs Decl. ¶ 44. However, when Dr. Kier reported Log P values for the methylpyridyl compounds and pioglitazone, he failed to account for all of the atoms in the compound because he omitted one of the methylene groups. Kier Decl. ¶¶ 62-66; Motion to Strike Exs. D and E (Gill Letters); Jurs Decl. ¶¶ 42-44. Put another way, Dr. Kier's analysis failed to account for the entire molecule, making his analysis inconsistent with his own description of what would be required to make the "fragment method" scientifically valid. As important, it is clear that the "remainder portions" of the molecules are not in fact identical.

Dr. Kier's admissions show that if all of the methylene groups had been accounted for in his "fragment method," rosiglitazone would fall outside the range framed by the methylpyridyls and hydroxyciglitazones. To make all of the remainder portions identical for the compounds Dr. Kier compared, one of the methylene groups in the 2-pyridyl TZD compounds (i.e., the methylpyridyls and pioglitazone) should be included in the terminal fragment. During discovery, Dr. Kier determined that the contribution of a methylene group to the overall Log P of a TZD compound for which there was no experimental value was 0.39 Log P units. Motion to Strike Exs. D and E (Gill Letters). If 0.39 Log P units were added to the

Log P value for the methylpyridyls framing the bottom of Dr. Kier's range (1.2), the range would become 1.59 to 1.82. As a result, the Log P of the rosiglitazone terminal fragment (1.43) would not be in that range.

Then, at his deposition, Dr. Kier opined that adding or subtracting a methylene group could affect a compound's Log P value by about 0.5 units:

> Q: And depending upon what fragments you use, you could get a different Log P value?
> A: Yes.
> Q: In fact, adding or subtracting a methylene group could affect it by .5, correct?
> A: Right. Ex. 57 (Kier Tr.) at 112:04-10.

Adding 0.5 units to the Log P value listed for the methylpyridyls (1.2) would change Dr. Kier's range to 1.7 to 1.8, and the rosiglitazone terminal fragment would again be outside Dr. Kier's "optimal range."

Finally, in his Declaration in Opposition to SKB's Summary Judgment Motion, Dr. Kier stated that for ciglitazone, the contribution of an additional methylene in the non-terminal linker portion of the molecule will be less than about 0.5, but he did not specify by how much. Kier Decl. ¶ 86.

In sum, Dr. Kier's opinions that the contribution to lipophilicity of a methylene group is 0.39 Log P units, 0.5 Log P units, or less than 0.5 Log P units provide further evidence that at the time rosiglitazone was invented, a person of ordinary skill in the art could not have determined the contribution to lipophilicity of a methylene group with any precision or certainty. This is significant because,

as Figure 1 shows, Dr. Kier's optimal lipophilicity range (1.2-1.8) is already narrow, spanning only 0.6 Log P units. However, Dr. Kier's admissions suggest that his range should be narrowed even further, by 0.39 to 0.50 Log P units[8] -- almost the entirety of the range -- and effectively eliminates the range.

c. Teva Has Not Shown by Clear and Convincing Evidence That The Remainder Fragments Make Virtually Identical Contributions to Overall Lipophilicity.

Teva also relies on Dr. Kier's opinion testimony that the influence on lipophilicity of a methylene group depends upon where it is located in the molecule, and specifically that a "non-terminal" methylene group – *i.e.*, one located in the middle of a molecule -- makes a smaller contribution to lipophilicity than does a "terminal" methyl group – *i.e.*, one located at the end of a molecule. Teva Suppl. Br. at 9; Suppl. Kier Decl. ¶ 3. Thus, Teva contends that one skilled art in 1987-88 would have understood that the unaccounted-for methylene, found in the middle of the molecule, would not have a meaningful effect on the lipophilicity of the entire TZD molecule and would therefore ignore it.

The Court concludes that Dr. Kier's opinion testimony and calculations in this regard are insufficient to create any genuine issue of material fact for trial.

At the outset, the Court notes that Teva's argument, which relies upon the contribution to lipophilicity of a "non-terminal" methylene group within the entire

[8] The increase from the 1.2 Log P value 0.39 to .050 means that the difference between 1.2 and 1.8 is less, *i.e.*, the range is narrowed.

molecule, is inconsistent with the undisputed fact that when Dr. Kier derived his optimal lipophilicity range, he treated "terminal fragments" as separate, complete compounds. Kier Decl. ¶ 62. For example, when determining his Log D range, Dr. Kier did not simply ignore the contribution to lipophilicity of a methylene (CH_2) group at the end of the rosiglitazone "terminal fragment" on the ground that, in rosiglitazone, the methylene is located in the middle of the molecule. Instead, Dr. Kier determined the Log P of a rosigliatzone "terminal fragment" that he treated as a complete compound having a "terminal methyl." *Id.* at ¶ 74. Therefore, to be consistent, while accounting for the omitted methylene for the various compounds he compared, Dr. Kier would have to add a methyl group to the "terminal fragments" of the methylpyridyls (and to pioglitazone) and then calculate a Log P for those fragments as if they were separate, complete compounds. Jurs Decl. ¶¶ 44-47. Neither Teva nor Dr. Kier address the issue of whether a person of ordinary skill in the art would have ignored the contribution to lipophilicity of the "non-terminal" methylene in the methylpyridyls (and pioglitazone) if the skilled person was using Dr. Kier's terminal fragment method, *i.e.*, if the "non-terminal" methylene was located in the terminal fragment and was treated as a complete compound, making it a "terminal" methyl.

The conclusion does not change even if the Court accepts Teva's argument that the proper focus is not the contribution to lipophilicity of the methylene group

in the "terminal fragment," but rather the contribution of the methylene in the whole molecule. As discussed above, SKB's summary judgment papers, and Dr. Kier's admissions showed, if the methylene group is accounted for when utilizing Dr. Kier's "fragment method," rosiglitazone falls outside of Dr. Kier's "optimal range" of lipophilicities. In response, Dr. Kier submitted a Supplemental Declaration in which he testified that in the context of a whole TZD molecule, the contribution to lipophilicity of a methylene group is 0.1 Log P units; thus, Dr. Kier's optimal lipophilicity range would change "only slightly" and the "non-terminal" methylene group would have been ignored by the person of ordinary skill in the art at the time of the invention in 1987-88. Suppl. Kier Decl. ¶¶ 4-6.

However, Dr. Kier determined the 0.1 Log P units value of a single methylene group in a TZD molecule by using a computer program (ChemDraw Ultra version 9.0.1) to calculate the difference between (a) the lipophilicity of an entire TZD molecule with one methylene group in the linker and (b) the lipophilicity of an entire TZD molecule with two methylene groups in the linker. Suppl. Kier Decl. ¶ 4. But, as stated above, it was not possible, at the time of rosiglitazone's invention, to calculate the lipophilicities of entire TZD molecules. Motion to Strike Ex. F (Kier Tr.) 82:11-24; Ex. 16 (Cantello 2) at p. 1184 n. 13. Indeed, Dr. Kier explained that it was because the Log P value of the TZD moiety was unavailable at the time that led him to use the "fragment method" in the first

place. Motion to Strike Ex. F (Kier Tr.) at 82:11-24; 6/28/2007 Hr'g Tr. at 61:08-11. At the summary judgment hearing, Teva's counsel admitted that the ChemDraw Ultra Version 9.0.1 computer program that Dr. Kier used to determine the 0.1 Log P unit value reported in his Supplemental Declaration was ***not*** available to a person of ordinary skill in the art at the time that rosiglitazone was invented. 6/28/2007 Hr'g Tr. at 61:08-11. Therefore, Dr. Kier's methodology is clearly hindsight. Where Teva cannot show by clear and convincing evidence that the calculations and methods Dr. Kier used to determine the 0.1 Log P unit value were in the prior art and available to a person of ordinary skill in the art at the time rosiglitazone was invented, they cannot be considered when determining obviousness. *Bausch & Lomb, Inc. v. Barnes-Hin/Hydrocurve, Inc.*, 796 F.2d 443, 449 (Fed. Cir. 1986).

Teva thus cannot show by clear and convincing evidence that a person of ordinary skill in the art would have been able to determine that the contribution to lipophilicity of a "non-terminal" methylene group in a TZD group is only 0.1 Log P units. Teva therefore also cannot show by clear and convincing evidence that a person of ordinary skill in the art would have ignored the contribution to lipophilicity of the methylene group that Dr. Kier left unaccounted for in his "fragment method" analysis.

To the contrary, Teva admits that all portions of a compound contribute to

its overall lipophilicity that the methylene group adds to the overall Log P of a compound. Under these circumstances, there exists no reasonable basis to conclude that a person of ordinary skill seeking to derive a precise lipophilicity range from which to make a novel TZD drug compound would have ignored the contribution to lipophilicity of one of the methylene groups in a prior art TZD derivative compound. There is therefore a failure of proof concerning an essential element of Teva's case.

d. Teva's Remaining Arguments And Evidence.

Teva's remaining arguments and evidence on this point do not present any material factual disputes that avoid summary judgment.

First, Teva argues that there is a material factual dispute because in Dr. Kier's method the terminal fragment is "defined as it is in the prior art," and that SKB is somehow "redefining what should be included in the terminal fragment." *See* Teva Opp. at pp. 5-6, 16, 21; Teva Rule 56.1 ¶¶ 30, 165; Kier Decl. ¶ 29. The Court's analysis, however, does not turn on labels. Rather, it is driven by the fact -- undisputed by the parties -- that all portions of a molecule contribute to lipophilicity and should be considered. Teva Rule 56.1 ¶ 64; Ex. 52 (Kier Tr.) at p. 100:12-15. Moreover, Teva's own descriptions of terminal fragments of TZD compounds are not consistent. When not calculating lipophilicities, Teva describes rosiglitazone and the prior art methylpyridyl and pioglitazone molecules as having

two methylene groups in the linker and none in the "terminal fragment." *See* Teva Opp. at pp. 5-6; Teva Rule 56.1 at ¶¶ 30, 94, 146. But, as shown above, when calculating lipophilicities of the terminal fragments of these compounds, Teva includes one of the two methylene groups as part of the "terminal fragment" in the case of rosiglitazone, but neither of the two methylene groups as part of the "terminal fragment" in the case of pioglitazone and the methylpyridyl compounds. *See* SKB Br. at pp. 26-31; Ex. 57 (Kier Tr.) at 107:06-12, 113:02-115:19; Ex. 58 (Kier Dep. Ex. 15).

Second, Teva argues that Dr. Kier's methodology is correct because the presence or absence of an additional methylene group does not make any difference to the activity of ciglitazone and hydroxyciglitazone. Teva Suppl. Br. at 8; Teva Rule 56.1 ¶ 162; Kier Decl. at ¶¶ 24-25. This argument, however, does not raise any genuine issue of material fact. First, that argument is inconsistent with Teva's admission and Dr. Kier's opinion that for 2-pyridyl containing compounds, "a two-carbon unit methylene linker fragment was optimal for eliciting strong activity for TZD derivative compounds." *See* Teva Rule 56.1 Statement ¶ 178; *see also* Kier Decl. ¶¶ 22, 44 (stating that a person of ordinary skill would have known that the two carbon unit methylene linker was optimal and would have retained it). More important, even accepting that the number of methylenes makes no difference to activity, Dr. Kier has not explained how or why it was proper for him

to omit methylene units when comparing/calculating the relative ***lipophilicities*** -- not ***activities*** -- of different compounds. When asked whether he could predict the effect of removing one of the two methylene groups from the linker in rosiglitazone, Dr. Kier admitted just the opposite:

> I don't believe I would want to attempt that because I really don't know exactly what the role of the terminal fragment is. In some cases it might interfere with absorption, promote it. It might produce other side effects, even metabolic effects, so there are too many things going on to jump into that, I think. Ex. 52 (Kier Tr.) at 141:19-42:01.

In sum, the Court concludes that Teva cannot show by clear and convincing evidence that at the time of rosiglitazone's invention, a person of ordinary skill in the art would have concluded that the lipophilicity of rosiglitazone lies between the lipophilicities of the methylpyridyls described in the '777 Patent and the hydroxyciglitazones described in the '902 Patent.

D. No Reasonable Trier Of Fact Could Find By Clear And Convincing Evidence That Claim 43 Of The '953 Patent Was Obvious

Teva also alleges that claim 43 of the '953 patent is invalid as obvious. The left side of DRG, the claim 43 compound, is the same as rosiglitazone, and is characterized by the presence of an unsubstituted 2-pyridyl ring and a methylamino group on the left side, which are not found in the prior art compounds. Thus, for all the reasons set forth above with regard to rosiglitazone, the prior art did not provide any motivation to make the DRG compound with a reasonable expectation of success, and Teva cannot meet its burden of proving that claim 43 is obvious.

IV. CONCLUSION

To preclude summary judgment, Teva must raise a genuine issue of material fact that supports (1) why and how a person of ordinary skill would have designed rosiglitazone from the prior art, common knowledge or common sense; and (2) that such a person would have had a reasonable expectation of success of making a TZD drug useful to treat Type 2 diabetes. Teva's lipophilicity-based theory of obviousness does neither. Accordingly, the Court grants SKB's motion for summary judgment that Claims 42 and 43 of the '953 patent are not invalid under 35 U.S.C. § 103.

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